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Sjögren's Syndrome

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Symbols and abbreviations

ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
AECG	American European Consensus Group
AIHA	autoimmune haemolytic anaemia
AIR	AutoImmunité et Rituximab
ANA	anti-nuclear antibody
BAFF	B-cell activating factor
BRAF-MDQ	Bristol rheumatic arthritis fatigue multi-dimensional questionnaire
CBT	cognitive behavioural therapy
CFS	chronic fatigue syndrome
CHB	congenital heart block
CK	creatine kinase
CMV	cytomegalovirus
CNS	central nervous system
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computerized tomography
DLBC	diffuse large B-cell
DNMT	DNA methyl transferase
dRTA	distal renal tubular acidosis
dsDNA	double stranded DNA
EBV	Epstein-Barr virus
EMG	electromyography
ENA	extractable nuclear antigen
ESR	erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European League Against Rheumatism
FACIT-F	functional assessment of chronic illness therapy fatigue subscale
FISH	fluorescent in situ hybridization
FNA	fine needle aspiration
FLS	focal lymphocytic sialadenitis
FSS	fatigue severity scale
fVAS	fatigue visual analogue scale

GC	germinal centre
HGP	hypergammaglobulinaemic purpura
HIV	human immunodeficiency virus
HLA	human lymphocyte antigen
HRCT	high resolution computed tomography
HRQoL	health-related quality of life
IBS	irritable bowel syndrome
ICER	incremental cost-effectiveness ratio
IFN	interferon
IPI	International Prognostic Index
IVIg	intravenous immunoglobulins
LDH	lactate dehydrogenase
LESA	lymphoepithelial sialoadenitis
LIP	lymphocytic interstitial pneumonitis
MALT	mucosa associated lymphoid tissue
MCII	minimal clinically important improvement
MCP	metacarpophalangeal
ME	myalgic encephalomyelitis
MFI	multidimensional fatigue inventory
MGD	meibomian gland dysfunction
MHC	major histocompatibility complex
miRNA	microRNAs
MRI	magnetic resonance imaging
mRNAs	messenger RNAs
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence
NSAID	nonsteroidal anti-inflammatory drugs
NSIP	non-specific interstitial pneumonia
OSDI	Ocular Surface Disease Index
PASS	patient satisfactory symptom state
PBC	primary biliary cirrhosis
PCR	polymerase chain reaction
PET	positron emission tomography
PNS	peripheral nervous system
PIP	proximal interphalangeal
PROFAD	profile of fatigue and discomfort
PROMS	patient reported outcomes
pSS	primary Sjögren's syndrome
RA	rheumatoid arthritis
RF	rheumatoid factor

RTA	distal renal tubular acidosis
SCLE	subacute cutaneous lupus erythematosus
SGEC	salivary gland epithelial cells
SICCA	Sjögren's International Clinical Collaborative Alliance
SL	sublingual glands
SLE	systemic lupus erythematosus
SM	submandibular glands
SNP	single nucleotide polymorphism
SS	Sjögren's syndrome
SSA	anti-Ro antibodies
SSB	anti-La antibodies
SSCAI	SS Clinical Activity Index
SSDAI	SS Disease Activity Index
SSI	Sicca Symptoms Inventory
SSDDI	Sjögren's Syndrome Disease Damage Index
sSS	secondary Sjögren's syndrome
TAP	transporter associated with antigen processing
TCAs	tricyclic antidepressants
TFBUT	tear film break-up time
TNF	tumour necrosis factors
TTG	tissue transglutaminase
US	ultrasound
SGUS	salivary gland ultrasound scan
UTI	urinary tract infection
UWS	unstimulated whole saliva
VAS	'visual analogue scales' or 'visual analogue scale'
WMH	white matter hyper-intensities

Chapter 1

Epidemiology, genetics, and disease burden

Simon Bowman

Key points

- Primary Sjögren's syndrome (pSS) is a worldwide disease, nine to 13 times more common in women than men, and typically presenting in the middle years.
- Its prevalence is estimated at 0.04–0.06% of the adult female population.
- The major genetic contribution to pSS is from the human leukocyte antigen (HLA) region, particularly the HLA-DR3.
- Additional genetic associations have been identified through modern genetic techniques. These include interferon-related genes, B-cell related genes, and TNIP1.
- PSS may also be affected by epigenetic factors such as DNA methylation and microRNA effects on cell regulation.
- Many studies on pSS have identified negative effects on health-related quality of life, as well as its impact on direct healthcare and other indirect costs.

Historical background and description

Sjögren's syndrome (SS) was described by Henrik Sjögren, a Swedish ophthalmologist, in 1933 [1]. He used the term 'keratoconjunctivitis sicca' to distinguish the ocular surface features from those seen in vitamin-A deficiency (xerophthalmia). The term 'xerostomia' is, however, used to describe oral dryness. Henri Gougerot, a French dermatologist, had previously described three patients with sicca syndrome and salivary gland atrophy in 1925 [2]. Jan Mikulicz-Radecki, an Austro/Polish surgeon described the histological features in 1892 [3]. As well as dryness of eyes and mouth, dryness of the trachea, skin, nose, vagina, and bowel are also common.

The distinction between primary SS (pSS) and secondary SS (sSS) was set out in the 1960s [4]. The link with mucosa associated lymphoid tissue (MALT) B-cell lymphoma was also reported [5] and Chisholm and Mason described their scoring system for the histological features of salivary gland biopsies in pSS [6]. The anti-Ro (SS-A) and anti-La (SS-B) antibodies were first identified [7] in 1969 and subsequently shown to be associated with pSS, HLA-DR3 and other human lymphocyte antigen (HLA) haplotypes [8] and the neonatal lupus syndrome [9].

The glandular features and management of pSS and sSS are generally regarded as being similar although fibrosis, for example, is a more typical feature in scleroderma-related sSS. Unless otherwise stated, this chapter will focus on pSS.

Epidemiology and prevalence

SS is a worldwide disease with a strong female bias—traditionally reported as 9:1 but possibly as high as 13:1 [10]. Typically, pSS presents in the fifth or sixth decade but can present at any age including, although rarely, in childhood.

Initial research into the prevalence of pSS came up with widely differing estimates as low as 0.08% (1 in 1,250) using the San Diego (California) criteria [11] or as high as 3% of the adult female population in a community-based study in the UK [12]. One explanation for this variation was the use of different, more permissive, classification criteria in the latter study.

More recent studies using the American-European Consensus Group (AECG) criteria have estimated the prevalence in women in the UK at 0.1–0.4% [13]. Other international studies using the AECG criteria have estimated the prevalence at around 0.2% [14] in the community and 0.04–0.06% in the hospital setting [15].

Classification criteria

In clinical practice it is up to the clinician to use their judgement in making a diagnosis of pSS. In research it is essential to have agreed classification criteria so that there is confidence that participants in a study have the specified condition. During the 1980s a number of classification criteria were proposed with a major debate as to the advantages and disadvantages of each of these criteria [16].

In 1988 a working group of 29 experts from 12 European countries initiated a study to develop consensus criteria and published their initial findings in 1993. The preliminary European criteria [17] included six components: symptoms of oral dryness identified through the presence of at least one out of three specified dry mouth questions and similarly for dry eyes, objective eye dryness, objective oral dryness, a positive labial salivary gland biopsy (≥ 1 focus score/4 mm^2), and positive anti-Ro/La antibodies. Four out of the six components were required to make a diagnosis of pSS. Exclusion criteria were also proposed (head and neck radiotherapy, hepatitis C infection, acquired immunodeficiency syndrome (AIDs), pre-existing lymphoma, sarcoidosis, graft-versus-host disease, and use of anticholinergic drugs). These criteria were subsequently modified to require the presence of either positive anti-Ro/La antibodies or positive labial salivary gland biopsy to form the AECG criteria [18] thus requiring evidence of an immunological basis for the dryness. The diagnosis of pSS is also fulfilled if three out of the four objective criteria are present. The criteria also propose that secondary SS is present if at least one oral or ocular symptom is present and two objective criteria (other than anti-Ro/La antibodies as these are not associated with sSS in rheumatoid arthritis (RA) or scleroderma).

The AECG criteria are the most widely used 'gold-standard' criteria for the classification of pSS in research studies. Criteria are never fixed in perpetuity, however, and as new technology such as ultrasound becomes more widely used or new data becomes available [19] further revision is likely. For example, one of the differences between the various criteria is whether to score a focus score of ≥ 1 or > 1 as positive and recent data suggests that the former is more closely linked with the clinical phenotype of pSS [20].

In 2013, an international collaboration, the Sjögren's International Clinical Collaborative Alliance (SICCA), funded by the National Institutes for Health in the US, collected data from 1,618 participants to devise the American College of Rheumatology preliminary criteria for SS [21] which requires at least two out of three components to be present, namely: (i) a positive labial salivary gland biopsy with a focus score of one or more; (ii) at least one positive antibody/combination out of anti-Ro, anti-La, or, the presence of both an ANA ≥1 in 320 and a positive rheumatoid factor; and (iii) dry eyes as determined by the presence of a new ocular staining score of ≥3. At the present time an international group of experts are bringing these criteria together to produce an American College of Rheumatology/European League Against Rheumatism consensus criteria.

Primary versus secondary Sjögren's syndrome

Both sets of criteria have similar exclusions. Individuals with another connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma are typically described as having 'secondary' SS as the development of SS is thought to be derived from the underlying pathophysiology of the 'primary' disease and is not usually associated with the extra-glandular features seen in patients with pSS. In rheumatoid arthritis, for example, individuals who develop sSS are more likely to be HLA-DR4 positive rather than the HLA-DR3 linked to pSS nor are they likely to have anti-Ro/La antibodies, but rather to be rheumatoid factor positive. In scleroderma, the salivary gland biopsies are more likely to demonstrate fibrosis. In other autoimmune or connective tissue diseases such as primary biliary cirrhosis it may be less clear cut whether SS is primary or secondary and is a matter for clinical judgement. The AECG criteria formally define secondary SS as the presence of at least one symptom of ocular or oral dryness plus at least one objective feature, or a positive labial salivary gland biopsy. Other exclusions for pSS include graft versus host disease, sarcoidosis, previous head and neck radiation, HIV or hepatitis C virus disease, pre-existing lymphoma, and the use of anticholinergic drugs accounting for the dryness features. Other conditions such as diabetes, bulimia, and chronic alcohol excess can lead to generalized swelling of the glands (sialosis). The preliminary American College of Rheumatology (ACR) criteria have added a relatively recently described condition 'IgG4 disease' among the excluded conditions [22].

Characteristic features of IgG4 disease include raised serum IgG4, IgG4-positive plasma cells infiltrating tissues, particularly the pancreas, causing autoimmune pancreatitis and the salivary glands resulting in swelling and/or dryness. The condition can also be associated with fibrosis (e.g. retroperitoneal). There is no female bias, no association with anti-Ro/La antibodies and generally, but not always, a good response to corticosteroid therapy. Some patients have been reported to have benefited from treatment with Rituximab.

Genetics, genomics, and epigenetics

Genetic risk factors

There have been no large-scale twin studies in pSS. Based on case reports and small studies the estimated concordance rate for SS is low and the sibling prevalence likewise, suggesting that the heritability of SS is low and environmental factors play a greater role

[23]. However, in a recent study by Kuo et al, of the 12,705 pSS patients, 105 (0.8%) had an affected relative. The calculated recurrence risk for a sibling or an offspring having pSS is approximately 19-fold and 13-fold higher than the general population.

PSS has been closely linked to the presence of particular genes of the human major histocompatibility complex (MHC) that encodes HLA proteins. These links are principally between the HLA types and the anti-Ro/La autoantibodies rather than with the disease per se. Patients with high levels of both anti-Ro and anti-La antibodies have a very high (circa 90%) likelihood of being HLA DR3 DQ2 positive (typically associated with the DRB1*03-DQB1*02-DQA1*0501 extended haplotype), whereas pSS patients who have high levels of the anti-Ro antibody only and are negative for anti-La antibodies have an increased frequency of DR2(15) and DQ6 (typically associated with the DRB1*1501-DQA1*0102-DQB1*0602 extended haplotype). Conversely, sSS in patients with RA is associated with HLA-DR4 [24], emphasizing that the clinical and histopathological similarities between pSS and sSS do not extend into identical genetic backgrounds.

Other potential genetic markers identified from candidate gene analyses include cytokine genes (e.g. for IL10, IL1 family, IL-6, TNF), MHC-related genes such as transporter associated with antigen processing (TAP) and tumour necrosis factors (TNF) and the Ro/La autoantigens themselves [25] (see Box 1.1).

Microarray technology can be used to genotype large numbers of single nucleotide polymorphisms whose frequency can be compared in thousands of cases and controls to identify novel associations between genes and disease for further study. In a study by Lessard et al in 2013 [26] using Illumina microarray technology of four datasets totalling 4,337 patient samples and 12,459 control samples the HLA region at 6p21 demonstrated the strongest association with the peak at HLA-DQB1. Other risk loci included IRF5, STAT4, IL-12A, BLK, CXCR5, and TNIP1 (Figure 1.1).

IRF5 is a transcription factor mediating type 1 interferon responses, STAT4 is a transcription factor for cellular responses initiated by type 1 interferons, and can be induced by IL-12 in some circumstances. BLK is a non-receptor Src family tyrosine kinase involved in B-cell receptor signalling and B-cell development whereas CXCR5 is a chemokine receptor for B-lymphocyte chemoattractant (BLC). IL-12 can induce CXCR5 expression potentially linking the two themes of type 1 interferons and B-cell activation. The function of TNIP1 is not fully described but is involved in NFkB regulation. In a study of single nucleotide polymorphisms in 1,105 patients and 4,460 controls an association was found between antibody-positive primary SS and two single nucleotide polymorphisms (SNPs) in TNIP1 [27].

Gene expression profiling using microarray technology can be used to identify genes that are over or under expressed in particular circumstances, which may be relevant to disease pathogenesis. In pSS (and systemic lupus erythematosus (SLE) and some other autoimmune disorders), one current theme, across a range of studies, is of overexpression of interferon (IFN) inducible genes, including Toll-like receptors, STAT4, IRF5, BAFF, and MECP2 [28, 29]. IFN is typically upregulated by viruses and this may

Box 1.1 Genetic risk factors in pSS

HLA
IRF-TNPO3
STAT4
IL-12A
FAM167A-BLK

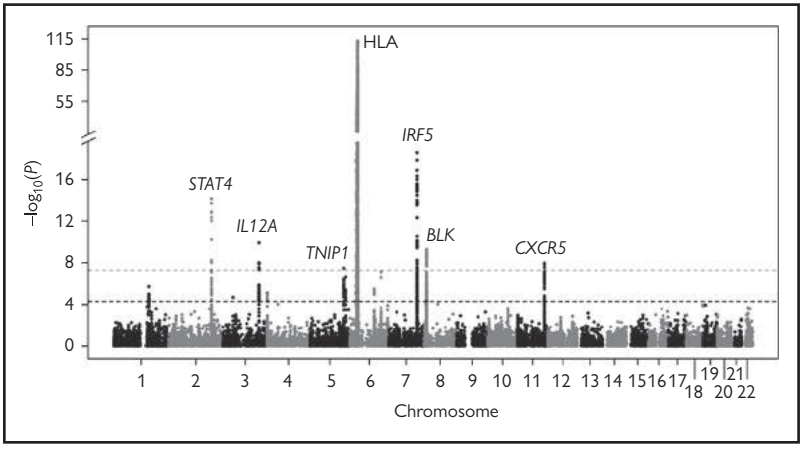

Figure 1.1 Summary of genome-wide association results for 27,501 variants overlapping between DS1 and DS2 after imputation and meta-analysis. The $-\log_{10}(P)$ for each variant is plotted according to chromosome and base pair position. A total of seven loci exceeded the GWS of $P_{meta} < 5\times10^{-8}$ (light grey dashed line). Suggestive threshold ($P_{meta} < 5\times10^{-5}$) is indicated by a dark grey dashed line.
Reproduced with kind permission from Lessard et al 2013; reference 26.

provide a link between the 'disease trigger' in these disorders and subsequent pathogenic processes.

Epigenetics

Another area that is currently of interest is that of 'epigenetics' which refers to processes such as DNA methylation or histone acetylation of DNA [30]. Such DNA modifications are potentially inheritable but do not alter the DNA sequence itself [31], can modulate gene expression patterns during cell development, the cell cycle, and biological/environmental changes. Disease-associated epigenetic alterations of gene expression could therefore theoretically contribute to pathogenesis of inflammatory diseases such as pSS. In general, DNA demethylation is associated with gene activation whereas DNA methylation is associated with gene inactivation (see Box 1.2).

Thabet et al 2013 [32] evaluated global DNA methylation within salivary gland epithelial cells (SGEC), peripheral T cells, and B cells from SS patients. Global DNA methylation was reduced in SGEC from SS patients, while no difference was observed in T and B cells. SGEC demethylation in SS patients was associated with a seven-fold decrease in DNA methyl transferase (DNMT) 1 and a two-fold increase in Gadd45-alpha expression. SGEC demethylation appeared to be at least partly related to the infiltrating B cells as it is reduced in patients treated with anti-CD20 antibodies to deplete B cells. Consistently, co-culture of human salivary gland cells and B cells led to an alteration of the PKC delta/ERK/DNMT1 pathway.

Altorok et al 2014 [33] performed a genome-wide analysis of DNA methylation in T-cells in pSS identified 311 demethylated genes including lymphotoxin-alpha, type-I interferon pathway genes, and genes encoding for water channel proteins and 115 hypermethylated gene regions including RUNX1 which may have a role in lymphoma predisposition.

In a study by Gestermann et al 2012 [34] there was no change in the methylation profile of the IRF5 promoter region, despite the known genetic polymorphisms.

Box 1.2 Epigenetic regulation of gene expression

Chromatin is found in the cell nucleus and is a nucleoprotein complex consisting of DNA wrapped around a core, which consists of histone proteins, along with enzymes and transcription complexes. The positive charge of histones partly counters the negative charge of DNA and allows the DNA to coil compactly into chromosome structure. Euchromatin describes loosely packaged chromatin, associated with high concentrations of genes and active transcription, whereas heterochromatin describes densely packaged chromatin with inactive genes. Switching between these states can therefore activate or inactivate gene expression.

There are several processes that can affect nucleosome dynamics and therefore gene expression by modulating the packaging of DNA in the nucleus and/or the binding of transcription factors. These include post-translational histone methylation, acetylation, phosphorylation, ubiquitination, sumoylation, ADP ribosylation, deamination, citrullination, protein conjugation, β-N-acetylglucosamination, and ion/protein binding to DNA. These processes are typically reversible. DNA methylation occurring on the 5' position of the pyrimidine ring of cytosines in the context of the dinucleotide sequence CpG forms one of the most important mechanisms controlling gene expression through altering chromatin structure.

Salivary gland acinar cells in SS show an altered attachment to the basal lamina and this may be linked to hypermethylation of the BP230 gene promoter region and reduced BP230 mRNA levels, and the authors hypothesize that this may link to cell survival [35]. Other apoptosis-related genes may also be differentially methylated [36]. These and other studies demonstrate the potential for DNA methylation and other processes to modify inflammation in pSS.

MicroRNA

Another process involved in cellular regulation is generated by microRNAs (miRNAs). These are small non-coding RNAs, 21–24 nucleotides in length. They are involved in degrading messenger RNAs (mRNAs) and disruption of translation. Interestingly, La antigen, a frequent autoantibody target in pSS, binds miRNA precursors and may regulate miRNA expression levels [37].

Alevizos et al 2011 [38], reported the differential expression of two miRNA in minor salivary glands of patients with pSS compared to controls. They showed that miR-768-3p was associated with increased salivary gland inflammation and miR-574 inversely so. Kapsogeorgou et al 2011 [39] also used comparative array analysis to demonstrate distinctive miRNA signatures in SS patients. Tandon et al 2012 [40] identified six new miRNAs from minor salivary glands in SS patients.

One miRNA involved in regulation of inflammation in RA, SLE, and psoriasis is miR-146a [41]. Pauley et al 2011 demonstrated increased miR-146a expression in the peripheral blood of 25 pSS patients as well as in the salivary glands of a mouse model of pSS. Zilahi et al 2012 [42] also found increased miR-146a (and miR-146b) expression by peripheral blood mononuclear cells.

Health-related quality of life and health economics

There have been extensive studies of health-related quality of life in pSS [43]. Quality of life is a broad concept of an 'individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their

goals, expectations, standards and concerns' (http://www.who.int/mental_health/media/68.pdf). Health-related quality of life (HRQoL) refers to the health domain but the subtleties are often blurred. The most widely used HRQoL questionnaire has been the 36-item Medical Outcomes Study SF-36 questionnaire covering eight domains. Although there are some differences between the studies in pSS the overall summary is that patients with pSS generally have reduced HRQoL across a range of SF-36 domains of similar extent to other rheumatic diseases such as RA or SLE. In a study in the US, somatic fatigue was the main predictor of physical function and depression of emotional well-being [44].

Another HRQoL measure that is increasingly being used due to its simplicity is the EuroQol 5-domain (EQ-5D) questionnaire. This comprises five domains; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as a global score. In the UK Primary Sjögren's Syndrome Registry, higher systemic disease activity (ESSDAI) scores and higher symptom scores (pain, depression, and ESSPRI) correlated with poorer HRQoL measured by EQ-5D [45].

As part of a UK study developing and validating symptom questionnaires in pSS alongside HRQoL measured by the SF-36, 129 female participants with pSS completed the economic portion of the Stanford Economic Assessment Questionnaire. This included information on direct healthcare costs such as visits to health professionals, in-patient stays, and investigation and drug costs based on 2004/5 UK Department of Health tariffs [46]. Using this approach the mean annual total direct costs per patient (95% confidence interval) was £2,188 (£1,831–£2,546) compared to £2,693 (£2,069–£3,428) for a comparator group of patients with RA and £949 (£741–£1156) for a community control group. This data predated the routine introduction of biologic therapies for RA and therefore likely would underestimate current costs for this group.

This study also collected data on indirect costs using a human capital approach to estimate time lost from the workplace or unpaid work at home [47]. Costs were estimated using average wages according to the Office of National Statistics (UK). Eighty-four patients with pSS, 87 with RA, and 96 community controls took part in this study. Twenty-five pSS, 36 RA, and 16 controls were over 65 (pSS versus controls $p = 0.037$ and RA versus controls $p < 0.001$). Twenty-six, 22, and 68 of the pSS, RA, and control patients respectively worked full or part time ($p < 0.001$ for pSS and RA versus controls). Using a conservative model for costs (95% confidence intervals) are £7,677 (£5,560–9,794) for pSS, £10,444 (£8,206–12,681) for RA and £892 (£307–1,478) for controls ($p < 0.001$ pSS or RA versus controls). Using maximum estimates the equivalent figures are £13,502 (£9,542–17,463), £17,070 (£13,112–21,028), £3,382 (£2,187–4,578), $p < 0.001$. For both direct and indirect costs, therefore, pSS comes out as approximately 70–80% of the equivalent costs for RA.

In terms of cost estimations the other critical one to consider is whether therapy improves patient HRQoL. Using EQ-5D to measure this allows estimation of the cost per quality-adjusted life year (incremental cost-effectiveness ratio (ICER)). In the UK, the National Institute for Health and Care Excellence (NICE) has used an ICER threshold of £20,000–30,000 to determine whether medications are cost effective for NHS approval. The TRACTISS study of rituximab versus placebo [48] includes EQ-5D and should allow for this calculation.

In general pSS is not associated with increased mortality, with the exception of patients who develop lymphoma [49, 50]. However, two recent reports have shown that the standardized mortality ratio of patients with pSS was increased compared to the general population. Additionally, there are very major effects on patients and their quality of life, which in turn has health-economic consequences.

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Conflicts of interest

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Chapter 2

Diagnosis and clinical assessment

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Key points

- The American European Consensus Group classification criteria is the most commonly used for Sjögren's syndrome (SS), but this is likely to be replaced by the American College of Rheumatology-European League Against Rheumatism criteria.
- Diagnostic work-up should include glandular and extra-glandular assessment and exclusion of conditions that may mimic SS.
- Structured assessment of both glandular and extra-glandular manifestations, including lymphoma development, should be carried out during routine clinic appointments.
- A multi-disciplinary approach is needed for optimal management of patients with SS.

Introduction

This chapter describes the clinical features of Sjögren's syndrome (SS), how a diagnosis of SS is established, and how patients with SS should be assessed in clinic. An overview of the pathogenesis and management of SS is also included for ease of reference. Detailed accounts of these topics are provided in other chapters of the book.

Pathogenesis

The aetiology of SS remains elusive. Genetic susceptibility and environmental triggers have been suggested to influence the development of SS. HLA-DR3/DQ2 haplotype is associated with the occurrence of anti-Ro/anti-La antibodies in pSS.[2] hepatitis C virus, human immunodeficiency virus (HIV), human herpes virus-6, human T-lymphotropic virus-1, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) have all been associated with an SS-like syndrome. Current evidence suggests that environmental or endogenous antigen triggers immune cell activation and autoantibody production, leading to a self-perpetuating inflammatory response in genetically susceptible individuals, and resulting in the destruction of exocrine glands.

Clinical features

Clinical features of SS may be present for up to ten years before a diagnosis is made. Initial manifestations include dry eyes and dry mouth, but clinical presentation may vary.

Sicca symptoms

Dry eyes and dry mouth, otherwise known as the sicca symptoms, are the most common symptoms of SS. 'Dry eyes' is commonly described as a gritty sensation in the eyes. Patients may also describe crusting of the eyelids on waking, stinging and redness of the eyes, blurred vision, and sometimes, paradoxically, 'watery' eyes. Xerostomia may present as altered taste perception, difficulty in swallowing and speech, poor denture retention, halitosis, dental caries, generalized oral discomfort with oral mucosal surfaces sticking together and to the teeth, and oral candidiasis with angular cheilitis.

Dryness can also affect nose, trachea, and pharynx. Intermittent salivary gland swelling is common in primary SS (pSS), but is less common in secondary SS (sSS). Recurrent parotitis may also occur.

Systemic involvement

Constitutional symptoms include fatigue, sweats, low-grade fever, and anorexia. Fatigue can be particularly disabling.

Musculoskeletal system

Articular manifestations are seen in 30% to 60% of pSS patients. Arthralgia is more common than overt inflammatory arthritis. Similarly, myalgia is common, whereas severe myositis is a rare occurrence, although mildly elevated serum creatinine kinase is not infrequent.

Pulmonary

Tracheobronchial mucosal dryness can manifest as dry cough and hoarseness of voice. Abnormalities in lung function tests, particularly in diffusion capacities and lung volumes can occur but are usually mild. Pneumonitis or bronchiectasis is a recognized association. Interstitial lung disease histopathology includes follicular bronchiolitis, lymphocytic interstitial pneumonia, and fibrosis with honeycombing. Severe pulmonary manifestations are rare.

Cutaneous

Dry skin is very common among patients with SS. Cutaneous vasculitis is a recognized but usually self-limiting condition. It usually affects small vessels but medium-sized vessels can also be affected. Small vessel vasculitis manifests as palpable purpura, urticarial lesions, or erythematous maculopapules. Necrotizing vasculitis of medium-sized arteries resembles polyarteritis nodosa. SS patients with high immunoglobulin levels may develop purpuric rash, often in the lower limbs. Subacute cutaneous lupus erythematosus and Raynaud's phenomenon can also occur.

Renal and genitourinary

Severe renal involvement is uncommon. Interstitial nephritis due to lymphocytic infiltration may lead to renal tubular acidosis. Patients may present with osteomalacia, renal stones, nephrocalcinosis, or hypokalemic paralysis (although rare). Immune complex glomerulonephritis can result in chronic renal insufficiency.

Urinary symptoms due to cystitis include dysuria and nocturia, frequent and urgent. Vaginal dryness, dyspareunia, and recurrent urinary tract infections are also common.

Neurological

SS can affect peripheral, autonomic, and central nervous systems. Peripheral neuropathy is being increasingly recognized as associated with SS. Sensory axonal neuropathy is the most common pattern but motor, mixed neuropathies and dorsal root gangliopathy can also occur. Mononeuritis multiplex and cranial neuropathies affecting trigeminal, optic, and facial nerves can occur. Autonomic symptoms are common such as sweating, postural hypotension, and dizziness.

Mild cognitive impairment and mental fatigue are often reported by pSS patients. White matter changes may be seen on imaging but severe CNS involvement is rare. Other CNS manifestations include multiple sclerosis-like syndromes, myelopathy, encephalopathy, optic neuropathy, and seizures. In patients with myelitis or optic neuropathy, neuromyelitis optica should be considered as a differential diagnosis.

Haematological and lymphoproliferative disease

Haematological manifestations are usually asymptomatic and can include anaemia, cytopenias, hypocomplementaemia, hypergammaglobulinaemia, paraproteinaemia, and raised acute phase reactants.

Anti-Ro (SSA) and anti-La (SSB) are the most commonly occurring autoantibodies in pSS. Anti-nuclear antibody (ANA) and rheumatoid factor (RF) may be positive, but are not specific to pSS. Other autoantibodies may also be present such as anti-centromere, anti-thyroid, and anti-phospholipid antibodies. Several autoantibodies (e.g. anti-muscarinic receptor type 3 and anti-α-fodrin) have been linked to pSS pathogenesis but tests for these autoantibodies are available only in research settings.

Lymphoma is 15–20 times more common in pSS patients than in the general population. Important predictors in the development of non-Hodgkin's lymphoma (NHL) include hypocomplementaemia (C3 or C4), cryoglobulinaemia, lymphopenia, low $CD4^+$ T-cell counts, persistent salivary gland enlargement, splenomegaly, lymphadenopathy, positive RF and cutaneous vasculitis [1].

Cardiac involvement

Cardiac involvement is rare. Pericarditis, pulmonary arterial hypertension, and left ventricular diastolic dysfunction have been documented.

Thyroid

Hypothyroidism is present in up to 20% of patients.

Gastrointestinal system and liver

Dysphagia due to pharyngoesophageal dryness is a common symptom. Gastroesophageal reflux disease occurs due to reduced saliva production and lack of acid clearance. Presence of helicobacter pylori should be excluded due to its association with mucosa associated lymphoid tissue (MALT) lymphoma in these patients. PSS is associated with coeliac disease, primary biliary cirrhosis, and autoimmune hepatitis. Although mild elevation of pancreatic enzymes has been noted in up to 37% of patients, serious pancreatic complications occur in only 1% of patients.

Box 2.1 Differential diagnosis of pSS	
Infective	HIV, hepatitis A, B or C, human T-cell lymphotropic virus 1 (HTLV-1), mumps, EBV, CMV, tuberculosis
Inflammatory/immune-mediated	Sarcoidosis, amyloidosis, IgG4-related disease
Malignancy	Lymphoma, other malignancy
Iatrogenic	Graft versus host disease, head and neck irradiation, medications
Endocrine/ Metabolic	Diabetes, acromegaly, alcohol excess, cirrhosis, lipoproteinaemia, bulimia, anorexia nervosa, endurance athletes, chronic pancreatitis.
Miscellaneous	Fibromyalgia, chronic fatigue syndrome, sialolithiasis, sialoadenitis.

PSS in pregnancy

SS patients who are pregnant and positive for anti-Ro (especially anti-Ro52) antibodies are at risk of recurrent miscarriages, complete heart block in the foetus, and neonatal lupus syndrome in the newborn.

Differential diagnosis

The list of differential diagnosis is extensive and includes other causes of dry mouth, fatigue, and salivary gland swelling (see Box 2.1).

Disease classification criteria

The most widely used classification criteria are the American European Consensus Group (AECG) classification criteria (2002) (see Box 2.2) [2].

For a pSS diagnosis, patients must meet either four of the six criteria including item IV (Histopathology) or VI (Autoantibodies), **or** three of the four objective criteria (III, IV, V, and VI).

Box 2.2 AECG (2002) classification criteria

I. Ocular symptoms: Dry eyes ≥ three months, foreign body sensation in eyes, use of artificial tears ≥ three times per day
II. Oral symptoms: Dry mouth ≥ three months, recurrent or persistent swollen salivary glands, need for liquids to swallow dry foods
III. Ocular signs: Schirmer's test ≤ 5mm per five mins, positive vital dye staining of eye surface
IV. Histopathology: Lymphocytic sialadenitis focal score ≥ 1 focus per 4 mm^2
V. Oral signs: Unstimulated whole saliva flow ≤ 1.5 ml per 15 mins, abnormal salivary scintigraphy, abnormal parotid sialography
VI. Autoantibodies: Anti-SSA/Ro or Anti-SSB/La

Exclusion criteria: History of head and neck radiation, hepatitis C infection, acquired immunodeficiency syndrome, sarcoidosis, amyloidosis, graft versus host disease, IgG4-related disease.

For a sSS diagnosis in patients with a major connective tissue disease, the presence of one symptom (I or II) plus two of the three objective criteria (III, IV, and V) is needed.

Work is in progress to harmonize the recently developed provisional American College of Rheumatology (ACR) criteria (2012), which is based on objective measures only, and the AECG criteria to improve the classification performance.

Diagnostic work-up for suspected cases of pSS

Basic investigations for patients with suspected pSS include history and examination, blood tests, urine dipstix, objective glandular function assessment, imaging, and minor salivary gland biopsy:

Blood tests

Full blood count

Urea and electrolytes

Liver and thyroid function tests

Creatinine kinase

Inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP))

Immunoglobulins and serum electrophoresis

Complement levels

Autoantibody screen (ANA, double stranded DNA (dsDNA), rheumatoid factor, and SSA and SSB, and extractable nuclear antigen (ENA) screen).

Objective glandular function tests

Lacrimal gland: Schirmer's I test (see Box 2.3)

Salivary gland: Unstimulated whole saliva flow (see Box 2.4).

Salivary gland function may be further assessed by salivary collection from individual major salivary glands, salivary scintigraphy, and sialochemistry.

Imaging

Salivary gland ultrasound scan (SGUS)

Chest radiography (if not performed within six months) to exclude sarcoid and tuberculosis.

Box 2.3 Schirmer's I Test

- Contact lenses should be removed prior to the test
- Anaesthetic eye drops* may be given prior to the test to prevent tearing due to irritation
- A strip of filter paper is folded at a right angle 5mm from the end. The small end of the filter paper is inserted into the lower lid
- The patient should close their eyes for the duration of the test.
- After 5 minutes the filter paper is removed from the eye

➔ More than 10 mm of moisture on the filter paper indicates normal tear production. A positive test for SS is ≤ 5 mm in 5 minutes.

Box 2.4 Unstimulated Whole Saliva Flow

- Patient should avoid any oral intake at least 1 hour prior to the test (water excluded). Smoking, chewing gum and coffee are also prohibited.
- Ask the patient to swallow then begin timing.
- Patient should then lean forward with eyes open and allow saliva to passively flow into collection tube.
- At the end of 15 minutes* the patient should collect all remaining saliva and spit into collection tube.
- Salivary flow should be weighed and calculated as grams per minute (g/min)**

➔ Salivary gland hypofunction is indicated when flow rate is ≤ 0.1g/min

* In clinic practice, the collection is sometimes being reduced to 5 minutes.

** 1 ml of saliva is presumed to weigh 1 g.

There is a growing body of evidence that USS of the salivary glands is both sensitive and specific for detecting glandular structural changes [3]. USS has the benefit of being non-invasive, and can easily be repeated for longitudinal follow-up. Magnetic resonance imaging (MRI) of the salivary glands should be considered if there is unilateral swelling of the salivary gland on examination to exclude lymphoma. Parotid sialography is now rarely performed but may show the presence of diffuse sialectasias without evidence of obstruction in the major ducts in patients with SS. It may be useful to exclude other causes of parotid gland swellings.

Biopsy

Minor salivary gland biopsy should be offered to all patients with suspected pSS. The histology sample is given a 'focus score'. The focus score and the presence of germinal centre-like structures in diagnostic salivary gland biopsies may be useful predictive biomarkers for non-Hodgkin lymphoma development [4].

Disease assessment: Disease activity and end-organ damage

A full clinical assessment of patients with SS should include the systemic (including lymphoma surveillance) and glandular manifestations of the disease. In addition, attention should also be paid to the impact of the disease on quality of life and functional capacity.

Systemic assessment

In the absence of specific biological disease activity markers, several assessment tools specific to pSS have been developed by the European League Against Rheumatism (EULAR) SS study group [5] and other researchers in recent years.

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) measures changes in disease activity in a number of systemic domains. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) assesses the extent and severity of symptoms (dryness, fatigue, and pain) in individual patients using 0–10 Likert's scales. EULAR sicca score (ESS) assesses overall symptom of dryness (Appendices 1–3).

Sjögren's Syndrome Disease Damage Index (SSDDI) and Sjögren's Damage Index (I) assess the accumulated, permanent morbidity due to the disease and side effects of treatment.

In clinical practice, the ESSDAI form a useful basis for conducting a structured review of the presence or absence of systemic manifestations in a pSS patient. The ESSDAI consists of twelve domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological, and biological. Recently, a modified version of ESSDAI (ClinESSDAI), without the biological domain, has been developed but has not been fully validated in clinical or clinical trial settings.

Ocular assessment

Ocular assessment should ideally be performed by an ophthalmologist. The Dry Eye Severity Grading Scheme is the most commonly used assessment tool.

Other clinical tests utilized by ophthalmologists include ocular surface vital staining (fluorescein, Lissamine green), tear film break up time, tear film osmolarity, and impression cytology.

Oral assessment

Xerostomia may be quantified by either stimulated or unstimulated salivary flow rates. A history of salivary gland swelling should be elicited, the salivary gland areas should be examined and the findings documented. Hard or unilateral parotid gland enlargement should prompt further investigations with urgent salivary gland ultrasound or MRI and referral for biopsy to exclude a tumour.

Management

Guidelines on the management of pSS are currently under development by the British Society for Rheumatology and the EULAR SS study groups. The following recommendations are based on a combination of the experience of the authors, expert consensus, and reported studies.

Ocular

Basic measures include:

- Avoid exacerbating factors of dry eyes (see Boxes 2.5 and 2.6).
- Provide advice on good eye care.
- Encourage regular optician review.
- Advise on tear substitutes.
- Advise on lid care (see the explanation of meibomian gland dysfunction below).

Replacement of tear volume palliates dry eye symptoms and may improve ocular surface disease. Tear substitutes act by reducing tear osmolality and lubricating the ocular surface. Preservative-free tear substitutes are recommended for frequent use

Box 2.5 Common factors that can exacerbate sicca symptoms

Dry environment (wind, air conditioning, central heating)
Irritants (dust, cigarette smoke, contact lenses)
Work or leisure activities (prolonged reading or computer use)
Food & Drink (alcohol, caffeine)
Medication (see Box 2.6)

Box 2.6 Common medications that can exacerbate sicca symptoms

Alpha blockers
Anticholinergics
Antidepessants (especially tricyclics)
Antihistamines
Antihypertensives
Beta blockers
Diuretics
Neuroleptics

as preservatives can exacerbate symptoms. Lubricating ointments for nocturnal use is advised.

Patients with severe refractory ocular dryness should be under the care of an ophthalmologist. Mucolytics may be considered for 'sticky eyes'. Topical glucocorticoids may be prescribed for ocular inflammation, but should be limited to 'pulsed' therapy to minimize risk of adverse effects (raised intra-ocular pressure, cataracts). Topical ciclosporin may also be considered under specialist guidance.

Punctal occlusion (by plugs or cauterization) preserves the tear film by retarding tear reabsorption.

Meibomian gland dysfunction is characterized by stinging, burning, and chronic inflammation of the eyelids. Patients should be advised to maintain lid hygiene: warm compresses, lid massage, and lid scrubs. A short course of antibiotic/steroid drops may be considered in the presence of inflammation. Prophylactic antibiotic drops at night may be used for recurrent conjunctivitis or blepharitis.

Oral

Basic management include:

- Robust oral and dental hygiene (including dentures).
- Encourage regular dental review.
- Encourage use of topical fluorides.
- Avoid exacerbating factors of xerostomia (see Boxes 2.5 and 2.6).
- Provide advice on saliva substitutes.
- Encrouatge regular sips of water.
- Advise on non-pharmacological measures to stimulate saliva production (sugar-free chewing gum, lozenges).
- Advise on the use of muscarinic agonists.

Saliva substitutes have a limited effect on symptoms of dry mouth, as they require repeated application due to swallowing and do not have the protective benefits of natural saliva. Some preparations contain fluorides and re-mineralizing solution, which may confer some dental protection.

Pilocarpine and cevimeline are muscarinic agonists. They stimulate glandular secretion and relieve the symptoms of xerostomia and xerophthalmia in patients with residual glandular function. Side effects include flushing, headache, nausea, diarrhoea, and urinary frequency. They should be avoided in patients with a history of ischaemic heart disease and uncontrolled asthma.

Systemic

Constitutional

Mild constitutional symptoms are frequent. If severe, lymphoma should be excluded. Hydroxychloroquine or a short course of corticosteroids may alleviate symptoms.

Musculoskeletal

Arthralgia and myalgia may be treated with analgesia, hydroxychloroquine, or short courses of oral corticosteroids where indicated. Evidence of other disease-modifying agents is poor. Myositis (raised creatine kinase (CK), confirmed on electromyography (EMG) or muscle biopsy) is treated with steroids, methotrexate, or other immunosuppressive therapies.

Respiratory

Treatment of respiratory manifestations depends on their severity. Corticosteroids or immunosuppression with cyclophosphamide is needed for significant interstitial/bronchial disease or reduced pulmonary function.

Neurological

Small-fibre (pure sensory) neuropathy can be treated with neuropathic analgesics (such as gabapentin, amitriptyline, pregabalin, and carbamazepine), although they may exacerbate sicca symptoms. Hydroxychloroquine may slow the progression of sensorimotor polyneuropathy.

Mononeuritis multiplex is treated with corticosteroids, cyclophosphamide, or intravenous immunoglobulins (IVIg).

Patients with severe autonomic symptoms should be referred to a specialist with expertise in the assessment and treatment of autonomic dysfunction. They should be advised to maintain adequate hydration, wear compression stockings, and avoid standing from sitting or lying too quickly. Midodrine or fludrocortisone may be tried in those with objective abnormal autonomic tests.

Treat central nervous system vasculitis with corticosteroids and cyclophosphamide. Suggested treatments are rituximab, plasmapheresis, and IVIg in refractory cases, particularly if related to systemic vasculitis or cryoglobulinaemia.

Cutaneous

Table 2.1 summarizes the management of cutaneous manifestations of pSS.

Genitourinary

Chronic cystitis may respond to cimetidine or low dose steroids. Correct renal tubular acidosis-associated electrolyte abnormalities with alkalis such as sodium bicarbonate or potassium citrate. Glomerulonephritis requires treatment with corticosteroids, cyclophosphamide, or plasmapheresis. Nephrotoxic drugs should be avoided in these patients.

Manage dyspareunia due to vaginal dryness with lubricating gels and pessaries. Local oestrogen preparations can also be prescribed in post-menopausal women.

Gastrointestinal

Gastro-oesophageal reflux can be treated with proton pump inhibitors and eradication therapy for those with Helicobacter pylori infections. Ursodeoxycholic acid is a useful treatment for co-existing primary biliary cirrhosis (PBC). Corticosteroids or azathioprine may be used in patients with autoimmune hepatitis.

Table 2.1 Management of Cutaneous manifestations of pSS	
Dry skin and pruritus	Topical emollients, antihistamines
Photosensitivity	Avoid prolonged sun exposure, use high factor sun block
Hypergammaglobulinaemia-associated purpura	Hydroxychloroquine, compression stockings
Raynaud's phenomenon	Avoid smoking and beta-blockers. Pharmacological treatments include calcium channel blockers, ACE-inhibitors and in severe cases, sildenafil and intravenous prostacycline
Cutaneous vasculitis	Elevation of the legs, avoidance of prolonged standing, simple analgesia. Dapsone or colchicine can be used for mild recurrent or persistent disease, whereas systemic corticosteroids or other immunosuppression (azathioprine, methotrexate, or cyclophosphamide) may be required for more severe disease. For those with cryoglobulinaemia, plasmapheresis, IVIg, or rituximab may be used.
Subacute cutaneous lupus erythematosus (SCLE)	Hydroxychloroquine, chloroquine, mepracrine, dapsone, corticosteroid (topical or systemic), methotrexate, thalidoamine, biological therapies
Note: Management of cutaneous vasculitis and SCLE should ideally have specialist input from dermatology.	

Haematological

Severe cytopenias require input of a haematologist and immunosuppressive treatment.

Fatigue

Screen for medical conditions which may contribute to fatigue. Patients should be given advice on sleep hygiene, avoiding exacerbating factors such as disturbed sleep, stress, and depression. Graded exercise regimes may be beneficial. Hydroxychloroquine may be tried but may take up to six to 12 months of treatment to obtain any benefit.

Pregnancy

Patients with anti-Ro antibodies who are pregnant should be closely monitored with weekly or fortnightly obstetric ultrasound scanning and echocardiography between 12 and 30 weeks of gestation, as this is the most common time for heart block to develop. Neonates should be delivered and cared for in a tertiary centre with cardiac pacing facilities available if required. There is some evidence for treating the mother with high dose dexamethasone or betamethasone in early pregnancy which can prevent foetal development of complete heart block.

Lymphoma

Patients should be educated about the signs and symptoms of lymphoma, which should prompt them to seek medical attention. High-risk patients should be reviewed on a six-monthly basis.

Investigation of lymphoma, regardless of type and stage should include MRI or computerized tomography (CT) imaging of the neck, chest, abdomen and pelvis, full blood

count, biochemistry, lactate dehydrogenase (LDH) level, serum protein electrophoresis, complement levels, paraproteins, β2m, IgM RF, immunoglobulins, and cryoglobulins. Where appropriate, bone marrow aspiration and biopsy, oesophageal-gastro-duodenal endoscopy with multiple biopsies and H. pylori testing. Pulmonary opacities should be investigated for bronchial MALT lymphoma. Positron emission tomography (PET) may also be useful.

Treatment is usually managed by a haemato-oncologist, and is tailored to the patient based on symptoms, site, grade, stage, and extent of lymphoma.

Emerging therapies

Data from early phase clinical trials have shown promising results for B-cell targeting therapies such as rituximab with improvement in disease activity scores, disease damage scores, and patient reported outcomes. Several other biological therapies targeting the dysregulated biological pathways in pSS are under development.

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Chapter 3

Oral features

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Key points

- In general, the principal causative factor underlying the subjective feelings and clinical findings associated with dry mouth is hyposalivation.
- The principal oral symptoms associated with hyposalivation are a tender oral mucosa; dry lips, cheeks, tongue, and palate; swollen salivary glands; increase in dental caries; and an increased susceptibility to oral infections.
- Patients with oral dryness complain of problems eating, swallowing, and with speech as well as having an urge to frequently moisten their mouth.
- Patients with Sjögren's syndrome are prone to develop B-cell lymphomas (predominantly mucosa associated lymphoid tissue lymphomas), often located in the parotid gland.
- Collection of saliva contributes to diagnosing Sjögren's syndrome, but is also helpful in determining a patient needs for oral treatment.
- Salivary gland sonography could be useful in diagnosing Sjögren's syndrome as well as monitoring its progression.
- Salivary gland biopsies (labial glands, parotid gland) are useful for diagnosing Sjögren's syndrome—including whether a patient has, or is at risk of developing, a B-cell lymphoma—as well as assessing treatment efficacy.
- Patients with Sjögren's syndrome require frequent visits to the dentist and/or dental hygienist (two to four times a year) to early diagnose and treat oral problems as well as to prevent development of dental caries and/or oral infections.
- Dental implants are not contraindicated in Sjögren's patients; they are very effective in oral rehabilitation of failing teeth.
- The treatment of B-cell lymphomas is dependent on the disease activity of Sjögren's syndrome.

Introduction

Kathy Morland Hamitt, a patient with Sjögren's syndrome, wrote in a book on dry mouth that when she visited her doctor the response she received was 'It looks like you suffer from dry mouth'. Hammitt then said, 'Really? Dry mouth?'. The reaction many patients who suffer from dry mouth often face a response like 'Is that all? Just a dry mouth? That can't be too bad' [1]. But how common is dry mouth? Brusquely stated, everyone at some time in their lives suffers from dry mouth, but mostly this is transient.

For instance, the relationship between dry mouth and stress has been known for centuries. The first time dry mouth was noted in medical literature was in 1868 when Dr AG Bartley wrote a letter to the *Medical Times and Gazette of London*:

I should feel obliged if you would give or procure me some advice in a case of *suppressed salivary secretion*. The patient, a quaint old French lady of 77, states that eight months ago she suffered about three weeks from dryness and soreness of the tongue. On examination of the mouth, uvula, tonsils and pharynx appear quite healthy, but *the mucous membrane is perfectly dry like pink satin*, that on the tongue with longitudinal rugae. Salt and sugar remain undissolved and quite *tasteless* on the tongue, the former causing slight uneasiness. The patient sips cold tea to relieve the feeling of dryness and the clinging together of gums, cheeks and tongue. *The teeth are all gone*. There is no discoverable opening in the parotid ducts. Under the tongue are two papillae where the sublingual ducts might be looked for, but they appear impervious. There does not seem to be any marked ill effect on health. The old lady is wonderfully well and cheery. Is there anything to be done? [Emphasis added.]

Bartley's description was very precious in describing four main attributes of severe oral dryness: hyposalivation, desiccation of the oral and pharyngeal mucosa, loss of taste, and the potential loss of teeth.

The main causes of oral dryness in today's life are the use of drugs (over 1,500 drugs are linked to a sensation of oral dryness), head and neck radiotherapy (ionizing radiation has to pass the salivary glands to reach the tumour), and SS. This chapter focuses on the oral sicca features resulting from SS and its treatment. Many of these features are not typical for SS, however, but are typical for salivary gland dysfunction in general.

Oral features of Sjögren's syndrome

The principal causative factor which underlies the subjective feelings and the clinical findings associated with dry mouth, is hyposalivation. Hyposalivation (the objectively measured reduction of salivary flow rate) and xerostomia, the sensation of a dry mouth, are often confused in literature, however. In this chapter we keep to the official definitions for xerostomia and hyposalivation as we have described.

Reductions in the flow of saliva as well as its qualitative changes predispose a patient, either directly or indirectly, to a variety of problems (Table 3.1). The severity of hyposalivation cannot be predicted with certainty from the patients' complaints, however. In general, the greater the reduction in the volume of saliva, the more severe the symptoms, but it is unclear how much saliva is required to maintain normal oral function. As a general rule, changes in salivary function over time are a more meaningful gauge of the impact of saliva on oral health than the actual salivary flow rate [2]. Generally speaking, an individual will experience oral dryness as soon as the level of salivary secretion in that person is reduced to below half of the level of salivary secretion that is normal for that individual at that time of the day. In other words, a certain level of salivary secretion can cause a sensation of oral dryness in the one person, while that same level of secretion is the basal level of salivary secretion for another person. Therefore, a person with, objectively, a moist mouth may complain about oral dryness, while another person with, objectively, a dry mouth may not experience oral dryness at all.

A reduction in the flow of saliva frequently causes difficulties with speaking, taste, and mastication (Table 3.1). Patients may have difficulty chewing and swallowing dry foods since they find it difficult to moisten their mouths. They are frequently thirsty, often sip water to facilitate deglutition, and may keep water by their bed at night. They may have difficulty in wearing dentures. Usually, there is a loss or a thinning of the layer of

Table 3.1 Symptoms associated with hyposalivation and dry mouth		
	Oral symptoms associated with hyposalivation	General symptoms associated with hyposalivation
Organs	**Mouth:** Soreness; oral mucosa is tender to acid and salty foods	**Nose:** Dry; frequent crust formation; nasal bleeding; decreased sense of smell
	Saliva: Scanty; thick, ropy, foamy; mucous accumulation	**Eyes:** Dryness; tingling, burning, itching, gritty sensations; feeling that lids stick together, sensitivity to light; blurred
	Lips: Dry, fissured; pebbled; peeling	**Throat:** Dryness; hoarseness
	Cheeks: Dry; rough; coated	**Gastro-intestinal tract:** Acid reflux; constipation; difficulty swallowing
	Tongue: Dry; fissured; pale or red; tingling/burning; sore; tongue may stick to palate	**Vagina:** Dryness; itching; burning; recurrent yeast infections; difficulty with intercourse
	Palate: Dryness; redness; tongue may stick to palate	
	Salivary glands: Swollen; obstructed; non-tender of painful	
	Teeth: Increase in dental caries; accumulation of dental plaque on soft surfaces and cervical area	
Functions/ Generalized symptoms	**Thirst:** Frequent sipping of water, especially when eating; liquids needed to taste food; need to keep water at bedside at night	Fatigue; Weakness; weight loss; depression; painful joints; multi drug use
	Mastication: Difficulty eating dry foods; difficulty with bolus formation; difficulty wearing dentures; difficulty swallowing; need to sip water while eating	
	Speech: Difficulty talking; hoarseness; tongue sticks to palate	

Modified from Sreebny LM, Vissink A. Dry mouth. The malevolent symptom: a clinical guide. Ames: Wiley-Blackwell, 2010.

mucin—which protects their oral mucosa—and patients may feel particularly sensitive to spicy foods. There may also be tingling and burning sensations of the oral mucosa, especially on the tongue. Moreover, the throat and oesophagus may be dry and there may be swelling of the salivary glands.

Extra-oral examination

Tender, relatively short-lasting swellings of the salivary gland(s) are suggestive of sialadenitis. This may be due either to a bacterial or viral infection, or due to an acute exacerbation of a chronic, usually bacterial, sialadenitis. Bacterial infections are often accompanied by a purulent discharge of the affected gland and are often very tender on palpation. Patients will present often with clinical signs of severe pain and (sub)febrile temperature. Infections due to viruses are also accompanied by a swollen, tender salivary gland, but no, or hardly any, saliva secretion is observed.

Chronic clinical indolent enlargements of the major salivary glands are quite common in SS. If these enlargements persist without periods of reduced enlargements or when the enlargements continue to grow, one has to be aware of the development of lymphomas (Figure 3.1). Lymphomas develop in 5% to10% of SS patients. In most cases, these are marginal zone B-cell lymphomas occurring in the salivary glands, in particular the parotid gland, so-called mucosa associated lymphoid tissue (MALT) lymphomas. Risk factors for the development of lymphomas are the presence of cryoglobulins, low complement C4 levels, recurrent or persistent swelling of salivary glands, and palpable purpura.

Intra-oral examination

Intra-oral clinical signs associated with oral dryness may be observed in the soft and the hard tissues of the mouth.

The oral mucosa may appear dry, atrophic, pale, or hyperaemic. The lips may be chapped or fissured and there may be scaling and fissuring at the corners of the mouth (angular cheilosis). The dorsum of the tongue may be dry and furrowed or, alternatively, may appear red, hyperaemic, and fissurized, often as a result of the presence of a fungal infection (Figure 3.2). The buccal mucosa may look pale and dry; tongue blades used to retract the cheeks which may stick to the mucosa. As with the tongue, it may appear red due to a yeast infection (especially, the candida species). Often no, or almost no, saliva can be elicited from the ducts of the parotid and submandibular glands, and adding citric acid to the tongue often result in, at most, some increase of salivary secretion if any (Figure 3.3). Also, there may be no evidence of the pool of saliva which is normally present on the floor of the mouth.

Figure 3.1 Enlargement of the left parotid gland in a patient with Sjögren's syndrome. Clinical palpation revealed that there were some nodules in the enlarged gland. The parotid biopsy and MRI revealed the presence of a MALT lymphoma.

Figure 3.2 Dry and fissured aspect of the dorsum of the tongue.

There is abundant evidence that xerostomia and hyposalivation commonly cause a marked, progressive increase in the incidence of dental caries; in many cases it is severe and rampant. The reduction in salivary secretion reduces the oral clearance of the oral surfaces. Moreover, the reduction in the volume of saliva is paralleled by alterations in the composition of the oral microflora. The change is primarily from a more alkaline one to a more acidogenic, cariogenic flora. It includes increases in the numbers of streptococcus mutans, lactobacillus species, actinomyces viscosus, streptococcus mitis, and, to a lesser degree, anaerobes. In addition, changes in the composition of saliva occur such as a reduction in the buffer capacity and pH of saliva, and a decline in the presence of the caries-preventive immunoproteins. These changes incur a rapid increase in the prevalence of hyposalivation-related dental decay (Figure 3.4). Without special care dental caries may progress extremely rapidly. In a severe dry mouth, a perfect dentition can be totally destroyed within months.

Some authors have reported an increase in periodontitis in patients with xerostomia and salivary hypofunction. This is an anomalous finding, however, since the ecology of the mouth is so different between periodontal disease and dental caries. Caries occurs in an acidogenic oral environment; periodontal disease in a more alkaline milieu. In our experience, periodontal disease is not increased in SS patients. Probably, when the oral hygiene is insufficient, progressive carious destruction is a much quicker process than periodontal decay and will have resulted in loss of teeth before periodontal decay has resulted in serious clinical signs.

How to assess oral features of Sjögren's syndrome

Collection of saliva

It may sound strange, but the single most constant feature of saliva is its variability. Its volume, its composition, and its viscosity fluctuate throughout the day. Its 'normal'

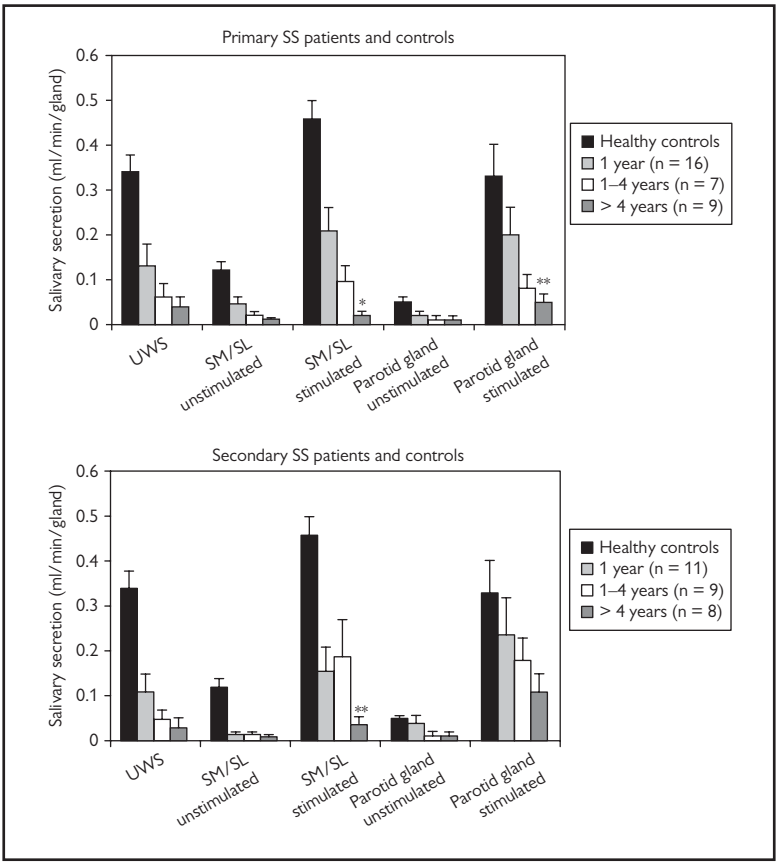

Figure 3.3 Relationship between disease duration (the time from first complaints induced by or related to oral dryness until referral) and mean (SEM) salivary flow rates in patients with (i) primary Sjögren's syndrome (pSS) and in those with (ii) secondary Sjögren's syndrome (sSS). Normal values are derived from historic controls (n = 36).

SM/SL, submandibular/sublingual glands; UWS, unstimulated whole saliva.

*Significant difference versus patients with early-onset Sjögren's syndrome (one-year oral complaints; $p < 0.005$) by the Mann–Whitney U test.

**Significant difference versus patients with early-onset Sjögren's syndrome ($p < 0.05$) by the Mann–Whitney U test.

Pijpe J, Kalk WWI, Bootsma H et al. Progression of salivary gland dysfunction in patients with Sjogren's syndrome. Ann Rheum Dis 2007;66:107–12.

values vary widely among people, which is also reflected by the level of salivary secretion that various subjects experience when they have a sensation of oral dryness.

The unstimulated secretion is significantly influenced by the time of day and year (circadian rhythms), by previous stimulation, by the position of the body, and by the patient's exposure to light and temperature. These are important, *controllable* variables that should be standardized for each patient when conducting sialometric tests. *Uncontrollable* variables that affect flow include gender, age, and weight of the patient, the size of the salivary glands, the patient's physical and mental health, and their intake of medications.

Figure 3.4 Hyposalivation-related dental caries. Due to the reduced oral clearance plaque is accumulating in the cervical regions of the teeth which makes these regions prone to rapid development of dental caries.

The collection and analysis of saliva is a non-invasive process. In general, *whole* saliva is the preferred indicator for overall mouth dryness and associated systemic disease; *gland-derived saliva* is more useful in the diagnosis of diseases of the salivary glands. Its collection takes little time, it is reliable, and it provides critically important data about oral and systemic health and disease.

The most common way to collect *unstimulated whole saliva* is the draining and spitting method. Patients are instructed not to do anything that will stimulate the flow of saliva for a period of at least 90 minutes before the collection time. This includes tooth brushing, the use of a mouthwash, drinking, chewing (e.g. food, gum), and smoking. The test should be conducted in a quiet area and the test methodology should be described to the patient prior to the collection procedure. The patient is then seated in the chair in an upright position with the head tilted down, is given a test tube, and is asked not to swallow. In the draining method, they are asked to sit quietly for five minutes, and then to allow the saliva to accumulate in the mouth and passively drain into the funnel (Figure 3.5). The volume of saliva is measured and the rate of flow is recorded in millilitres per minute (mL/min) (where 1 ml saliva = 1 g). The spitting technique is similar to the draining method, but the accumulated saliva is periodically expectorated into a tube.

Stimulated whole saliva

Stimulated whole saliva is collected after stimulation by either mastication or taste. A masticatory stimulus is given to the patient, which is either a piece of paraffin wax, gum base, or Parafilm® that they have to chew for five minutes. The accumulated saliva is then actively spit into the collected vessel every minute. The gustatory method utilizes a 2% (w/v) solution of citric acid to stimulate flow. The solution is applied to the lateral borders of the tongue with a cotton applicator every 30 seconds for five minutes. As with the chewing method, the saliva is expectorated into the collecting vessel every minute.

Glandular saliva

Glandular saliva is collected by means of a Lashley (Carlson-Crittenden) cup for parotid saliva and with an aspirator syringe for submandibular/sublingual saliva (Figure 3.6). The

Figure 3.5 Collection of whole saliva. The subject is seated comfortably with their eyes open and head tilted slightly forward. For resting saliva, the patient allows the saliva to accumulate in the mouth and then drains or spits it into the collection vessel, one to two times per minute for a period of five minutes. For stimulated saliva, paraffin wax, citric acid, or Parafilm® is used as a stimulant.

most commonly applied stimulus is a 2–4% (w/v) citric acid solution. This is applied to the lateral borders of the tongue at 30- or 60-second intervals with a cotton swab. It is usually collected over a period of ten minutes.

By using glandular saliva, patients with SS may be diagnosed at an earlier stage and progression and/or effects of therapeutic intervention can be measured in a non-invasive way (Figure 3.3). Early in the disease the secretion of submandibular/sublingual saliva is already reduced, while the glands are still able to produce reasonable amounts of parotid saliva upon stimulation. This phenomenon also matches the pattern of complaints of early SS patients: these are of oral dryness during sleep and at rest, while eating is not affected.

Sialography

Sialography is the radiographic imaging of the salivary duct system following the retrograde ductal infusion of oil- or water- based iodine contrast fluid. The main sialographic characteristic of SS is a diffuse collection of contrast fluid at the terminal acini of the ductal tree. This has been termed 'sialectasia' or sialectasis. Sialectasia ('cherry blossoms', 'snowflakes', or 'Apfelblüten') is classified as a punctate lesion if it is less than 1 mm in size; as a globular lesion if it is uniform and 1–2 mm in size; as cavitary if it is coalescent and > 2 mm in size; and as destructive if the normal ductal structures are no longer visible (Figure 3.7).

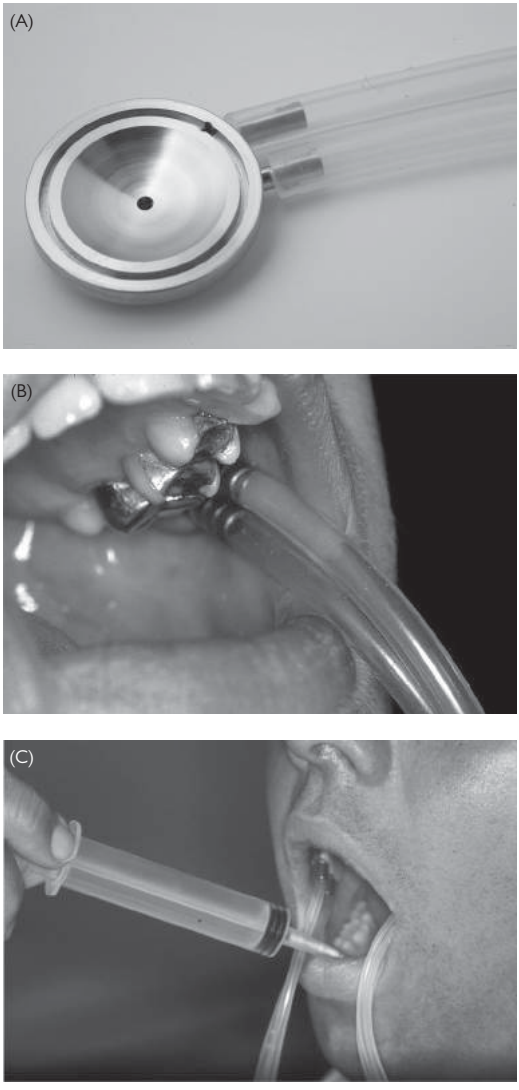

Figure 3.6 (A) The Lashley cup for collection of parotid saliva. The cup consists of an inner and outer chamber. The inner chamber serves as the collection chamber; the outer chamber is for suction.
(B) The cup is put in place over the orofice of the parotid duct (in the cheek, at the level of the second upper molar). The flow of parotid saliva is clearly visible in the tubing.
(C) Suction method for collection of submandibular/sublingual saliva. The orifices of the parotid ducts can be blocked with, for example, Lashley cups (as shown) or cotton rolls. The saliva collected in the floor of the mouth is now mainly submandibular/sublingual saliva and can be collected with a syringe.

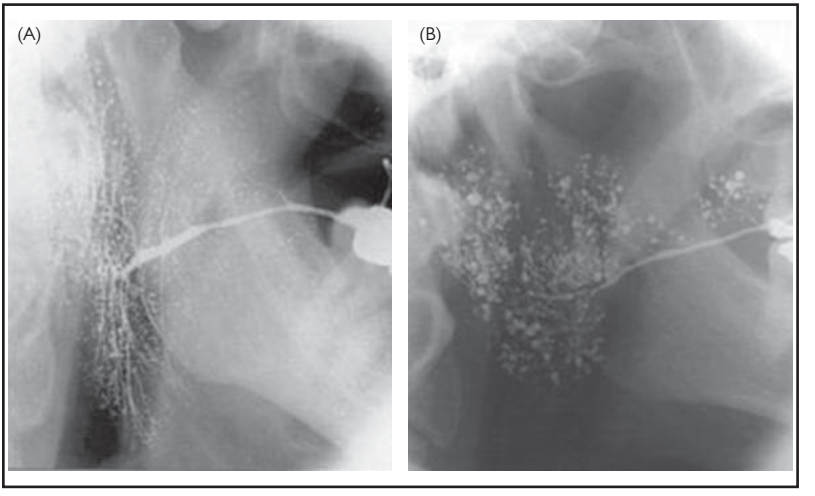

Figure 3.7 (A) Sialographic image of a healthy parotid gland. No sialectasia are seen. (B) Sialographic image of the parotid gland of a patient with Sjögren's syndrome. Globular sialectasia are seen.

Salivary scintigraphy

Salivary scintigraphy is based on the ability of the parotid and submandibular glands to trap the radionuclide isotope technetium-sodium (Tc^{99m}) pertechnetate. Tc^{99m} replaces the chloride ion in the active sodium/potassium/chloride co-transport pump that is located in the striated ducts of the salivary glands. In SS, the uptake and secretion of Tc^{99m} pertechnetate are reduced.

Sonography

Ultrasound waves may reveal parenchymal inhomogenity of the salivary glands. A characteristic alteration ('pepper-and-salt appearance') is used to describe sonographic images of patients with SS (Figure 3.8). The hypo-echoic areas in the salivary parenchyma are either considered to represent local lymphocytic infiltrates or dilated ducts

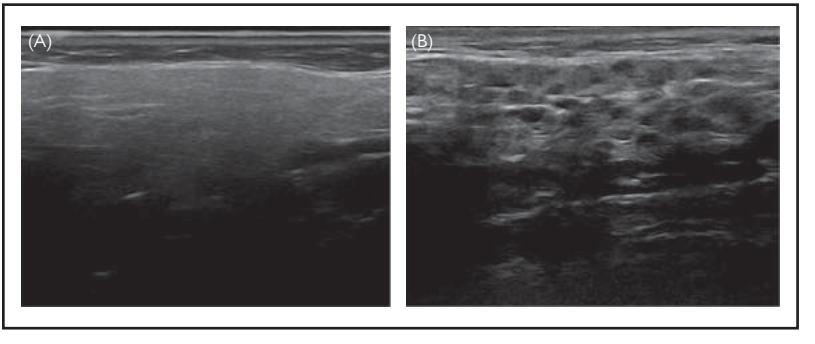

Figure 3.8 (A) Ultrasound image of a healthy parotid gland. (B) Ultrasound image of the parotid gland of a patient with Sjögren's syndrome showing the characteristic 'pepper-and-salt appearance'.

surrounded by dense lymphocytic infiltrates. How specific the ultrasound image is for SS has yet to be determined [3]. Nevertheless, work is ongoing to investigate whether salivary gland ultrasound should be incorporated in the classification criteria sets for SS.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) images of the salivary glands in patients with SS characteristically reveal the presence of hypo- and/or hyper intense nodules. MRI is mainly used to screen salivary glands for presence of lymphomas when applicable (Figure 3.9).

Sialendoscopy

Sialendoscopy permits the endoscopic intraluminal visualization of the ductal system of the major salivary glands and offers mechanisms to diagnose and treat both the inflammatory and obstructive pathology related to the ductal system. Besides detection and removal of sialoliths, ductal strictures can be resolved, mucous plugs can be removed, and the ductal system can be rinsed.

Salivary gland biopsy

Histopathology of salivary gland tissue is often helpful in the final diagnosis of oral dryness. The histopathologic criteria for the diagnosis of SS include the presence of clusters of lymphocytes of 50 or more cells per 4 mm^2, the so-called foci. Presence of ≥1 focus per 4 mm^2 salivary gland tissue is indicative of SS [4].

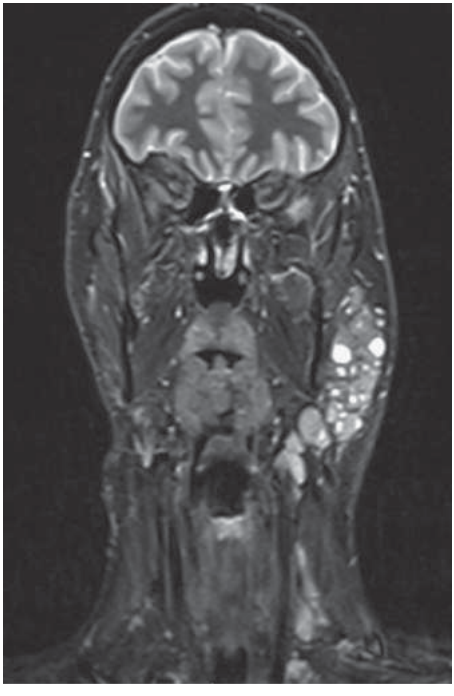

Figure 3.9 MRI image of a Sjögren's patient showing an enlarged left parotid gland with cyst-like lesions.

Figure 3.10 Labial biopsy. After a horizontal incision the labial salivary gland is exposed [4].
Delli K, Vissink A, Spijkervet FKL. Salivary gland biopsy for Sjögren's syndrome. Oral Maxillofac Surg Clin North Am 2014;26:23–33.

Labial biopsies are commonly performed under local anaesthesia (Figure 3.10). A lower lip mucosal incision of approximately 1 cm is made and at least seven individual labial glands are excised from the lower lip. Parotid gland biopsies can also easily be performed under local anaesthesia (Figure 3.11). A 1 cm skin incision is performed around the lower earlobe. After blunt dissection to the parotid gland, an incisional biopsy can be taken. The wound is closed in layers. No post-operative drape is needed. Pijpe et al showed that an incisional biopsy of the parotid gland is a safe and effective procedure in the diagnostic work-up of SS [5]. It may even be considered superior to a labial biopsy as it may cause less long-term morbidity and offers the possibility for repeated biopsies of the same gland. It is not uncommon to observe (early stages of) malignant lymphomas (MALT, non-Hodgkin lymphomas) in parotid biopsies [6].

Management of oral dryness features related to Sjögren's syndrome

The treatment of xerostomia and salivary gland hypofunction should be based on the answers to the following determinations [1]:

1. The cause of the dry mouth. If the cause can be *determined*, it should be eliminated. This may of course abate the problem, and it also may diminish the symptoms that are consequentially associated with a dry mouth. However, in the case of SS, the symptoms cannot be eliminated so far.
2. If the cause cannot be assessed or if treating the cause only partially relieves the oral dryness, *determine* if it is possible to stimulate the flow of saliva. This, per se, may readily diminish the oral desiccation (this is often the case in early stages of SS).
3. If the saliva cannot be adequately stimulated, *determine* whether one can combat the arid feeling by 'coating' the surfaces of the oral mucosa (this is often the case in advanced stages of SS).
4. *Determine* what else can be done to preserve and protect the teeth and the oral soft tissues and provide relief to the patient (this is common in early and advanced SS).

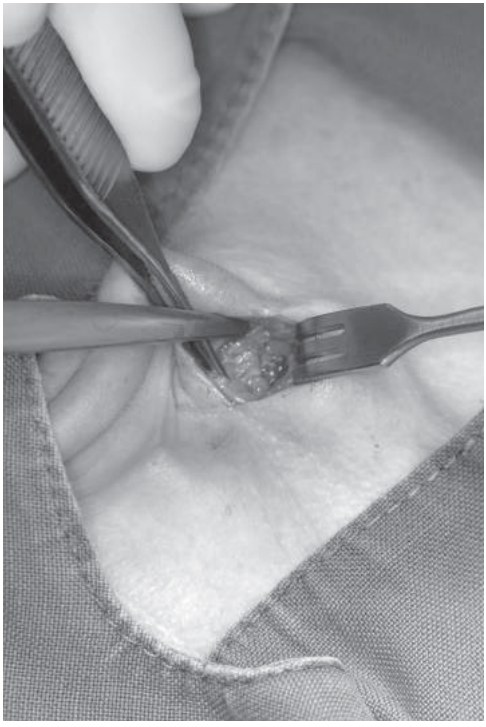

Figure 3.11 Parotid biopsy. The skin is incised and the tissue is dissected until the capsule of the parotid gland is reached. After opening the capsule, the parotid gland is exposed.

Relief of oral dryness

Frequent sips of water during the day can be the easiest and most efficacious technique to improve symptoms of dry mouth in some patients (Table 3.2). A slice of lemon or lime can be added to a glass of water to produce a mild acidic flavour that will enhance salivary output from the major salivary glands. Patients should be advised, however, that aqueous solutions do not produce long-lasting relief from oral dryness. Water wets the mucosa, but its moisture is not retained since the mucous membranes of xerostomic patients are inadequately coated by a protective glycoprotein layer [7].

Masticatory, gustatory, and mild acid stimulation techniques

Stimulation will only work if there are residual viable salivary gland cells that are amenable to stimulation (Table 3.2). In patients with long-term SS, the acinar fluid-producing cells may have already have been replaced by non-fluid producing connective tissue.

Masticatory stimulatory techniques are easy to implement and have few side effects. The combination of chewing and taste, as provided by gums, lozenges, or mints can be very effective in relieving symptoms for patients who have remaining salivary function. They are acceptable to most patients and are generally harmless (assuming that they are all sugar free).

Table 3.2 Management strategies for oral manifestations of Sjögren's syndrome

	Management strategy	Measures
Preventive measures	Regular dental visits and radiographs	• Usually every 3–4 months: dentist–oral hygienist–dentist–oral hygienist
	Optimal oral hygiene	• Guidance of team of oral-health professionals (clinical instructions, written instructions)
	Topical fluorides and remineralizing solutions	• Fluoride mouth rinse (0.1%, weekly) • Neutral sodium fluoride gel (depending on the level of oral hygiene and residual level of salivary flow: from once a week to every second day; the gel is preferably applied with a custom-made tray)
	Diet modifications	• Non-cariogenic diet • Minimize chronic use of alcohol and caffeine (increases dry sensation and itches oral mucosa) • Use of non-fermentable dietary sweeteners (xylitol, sorbitol, aspartame or saccharin), whenever possible
	Avoidance of drugs that may worsen sicca symptoms	• Common with use of antidepressants, antihistamines, anticholinergics, antihypertensives, neuroleptics
	Treatment of other medical conditions that result in xerostomia	• For example, endocrine disorders, metabolic diseases, viral infections
	Avoidance exacerbating factors	• Low-humidity atmospheres such as air-conditioned stores, centrally heated houses, windy locations • Irritants such as dust and cigarette smoke
Local salivary stimulation	Masticatory stimulatory techniques	• Sugarfree gums and mints
	Combined gustatory and masticatory stimulatory	• Lozenges, mints, candies • Water
Systemic salivary stimulation	Parasympathomimetic secretogogues	• Pilocarpine (5–7.5 mg, 3–4 times/day) • Cevimeline (30 mg, 3 times/day)
	Biologicals (not just for preservation of salivary secretion, focus is on treatment of systemic features; see treating underlying disorder)	• Rituximab • Abatacept • Belimumab
Symptomatic treatment	Relief of oral dryness (non-responders on systemic salivary stimulation)	• Air moisturisers • Frequent sips of water • Oral rinses, gels, and mouthwashes • Saliva substitutes

(*continued*)

Table 3.2 Continued		
	Management strategy	Measures
	Oral candidiasis	• Topical antifungal drugs: - Nystatin oral suspension (100,000U/ml: 400,000–600,000 units 4–5 times/day) - Clotrimazole cream (1%,2 times/day) - Ketoconazole cream (2%,1–2 times/day) - Amphotericin or rinse (100 mg/ml, 1 ml 4 times/day) • Systemic antifungal drugs: - Fluconazole tablets (200 mg on day 1,then 100 mg/day for 7–14 days) - Itraconazole tablets (200 mg/day for 1–2 weeks) - Ketoconazole (200–400 mg/day for 7–14 days) • Dentures should be soaked in chlorhexine (2%) at night
	Angular cheilitis	• Nystatin cream or ointment (100,000 U/g, 4–5 times/day) • Clotrimazole cream (1%, 2 times/day) • Miconazole cream (2%,1–2 times/day)
Treating underlying disorder	Systemic anti-inflammatory or immune modulating therapies to treat the autoimmune exocrinopathy of Sjögren's syndrome	• Anti-CD20 resulting in B-cell depletion (rituximab) • Targeting B-T cell interaction (abatacept) • Targeting B-cell activating factor (belimumab)

Modified from Meiners, PM, Meijer JM, Vissink A, Bootsma H. Management of Sjögren's syndrome. In: Weisman MH, Weinblatt ME, Louie JS, Van Vollenhove R. Targeted treatment of rheumatic diseases. Saunders: 2010:133–55.

Drugs

Two secretagogues, pilocarpine and cevimeline, have been approved by the US Food and Drug Administration (FDA) for the treatment of dry mouth (Table 3.2). Cevimeline is not yet available in Europe. Both drugs are muscarinic agonists that, in patients who have residual functional salivary gland tissue, induce a transient increase in salivary output and decrease their feeling of oral dryness. Common side effects include sweating, flushing, urinary urgency, and gastrointestinal discomfort.

Recently, some relief of oral dryness has been reported with the use of so-called 'biologicals' in patients with pSS. Amongst others, rituximab (directed towards the CD20 antigen on B-cells), abatacept (a drug inhibiting the T-B-cell interaction), and belimumab (a drug targeting B-cell activating factor (BAFF)) have been shown to reduce fatigue, but also have a beneficial effect on oral and ocular dryness [8].

What to do when stimulants fail?

Water, although less effective than the patients' natural saliva, is by far the most important fluid supplement for dry mouth individuals (Table 3.2). Patients should be encouraged to sip water and rinse it around their mouth throughout the day. This will help to moisten the oral cavity, hydrate the mucosa, and clear debris from the mouth.

There are numerous oral rinses, mouthwashes, and gels available for dry mouth patients. Patients should be cautioned to avoid products containing alcohol, sugar, or strong flavourings that may irritate the sensitive, dry oral mucosa. Moisturizing creams can also be very helpful. The frequent use of products containing aloe vera or vitamin E should be encouraged.

There are a variety of salivary substitutes commercially available, which have demonstrated some efficacy in dry mouth patients. However, saliva replacements (saliva substitutes or 'artificial salivas') are not well accepted long term by many patients, particularly when not instructed properly. As a guide to choosing the best substitute for a patient, the following recommendations for the treatment of hyposalivation can be used [9]:

- Severe hyposalivation: A saliva substitute with gel-like properties should be used during the night and when daily activities are at a low level. During the day, a saliva substitute with properties resembling the viscoelasticity of natural saliva—such as substitutes that have xanthan gum and mucin (particularly bovine submandibular mucin)—as a base should be applied.
- Moderate hyposalivation: If gustatory or pharmacological stimulation of the residual salivary secretion does not ameliorate the dry mouth feeling, saliva substitutes with a rather low viscoelasticity, such as substitutes which have carboxymethylcellulose, hydroxypropylmethylcellulose, mucin (porcine gastric mucin), or low concentrations of xanthan gum as a base are indicated. During the night or other periods of severe oral dryness, the application of a gel is helpful.
- Slight hyposalivation: The salivary glands of these patients usually contain viable, responsive acinar cells. Gustatory or pharmacological stimulation of the residual secretion is the treatment of choice. Little amelioration is to be expected from the use of saliva substitutes.

Regular dental visits and radiographs

Patients with salivary gland hypofunction require frequent dental visits, preferably every three to four months, and must work closely with their dentist and dental hygienist to safeguard dental health, a condition which is not so easy to maintain in SS patients. It is advised to follow sequenced visits that conform to the following order: dentist; dental hygienist–dentist–dental hygienist.

Oral hygiene

It is essential that patients with salivary gland disorders maintain meticulous oral hygiene. Proper oral hygiene includes tooth brushing, flossing, the use of interproximal plaque-removing devices, and the use of mouth rinses. Interdental brushes and mechanical toothbrushes are helpful for those with gingival recession and oral-motor or behavioural complications. Regular brushing of the tongue with a toothbrush or a tongue scraper is also recommended.

Topical fluorides and remineralizing solutions

The use of topical fluorides in a patient with salivary gland hypofunction is absolutely critical to the control of dental caries. There are many different fluoride therapies available, from low-concentration, over-the-counter fluoride rinses, to more potent highly concentrated prescription fluorides (e.g. 1.0% sodium fluoride). These are applied using a brush or in a custom-fitted carrier. The dosage chosen and the frequency of application (from daily to once a week) should be based on the severity of the salivary hypofunction and the rate of caries development [10].

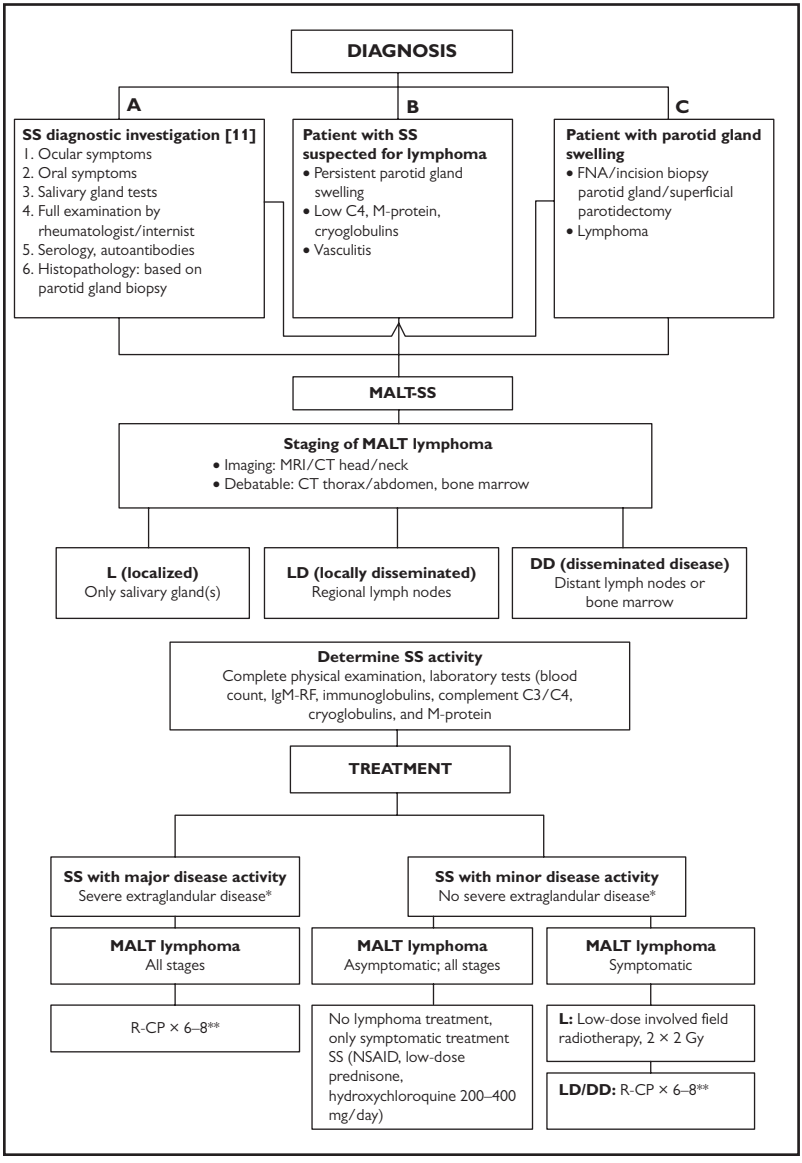

Figure 3.12 Management of MALT lymphoma of parotid gland and associated Sjögren's syndrome (MALT-SS). FNA: fine needle aspiration; R-CP: rituximab with cyclophosphamide and prednisone; NSAID: nonsteroidal anti-inflammatory drugs [6].

*Extra-glandular disease: poly-arthritis/myositis, glomerulonephritis, nervous system involvement, cryoglobulinemic vasculitis, other severe organ involvement, serological abnormalities: cryoglobulinemia, C4 < 0.10 g/l.

**Six intravenous infusions of 375 mg/m^2 of rituximab and six to eight cycles of cyclophosphamide, given every three weeks.

Oral candida therapy

Patients with dry mouth also experience an increase in oral infections, particularly mucosal candidiasis. A high index of suspicion for fungal disease should be maintained, and appropriate antifungal therapies should be instituted as necessary (Table 3.2). Patients with salivary gland dysfunction may require prolonged treatment to eradicate oral fungal infections.

Dental implants

Patients with SS may benefit from dental implants. The implant survival rate is comparable to that of healthy subjects. Peri-implant mucositis, but not peri-implantitis, is slightly increased compared to healthy subjects, probably due to the reduced oral clearance which promotes accumulation of plaque around the implants [12].

Management of salivary gland swelling in Sjögren's syndrome

Five to 10% of patients with SS develop a malignant B-cell lymphoma, 48% to 75% of which are of the MALT type. These B-cell lymphomas are most frequently located in the parotid gland. A study showed a 6.6-fold increase of non-Hodgkin lymphoma (NHL) in SS patients as compared to controls [13]. MALT lymphoma of the parotid gland is almost exclusively associated with SS.

MALT lymphoma in general is an indolent disease, with a reported five-year overall survival rate between 86% and 95%, without significant difference in clinical course between localized and disseminated disease. Recurrences may involve extra-nodal or nodal sites. Progression to aggressive lymphoma is rare, occurring in less than 10% of cases.

The diagnostic work-up should consist of parotid gland incisional biopsy, and when positive, MRI imaging of the head and neck area and CT-scan of the thorax and abdomen for dissemination diagnostics. If dissemination is detected, a bone marrow biopsy should be taken.

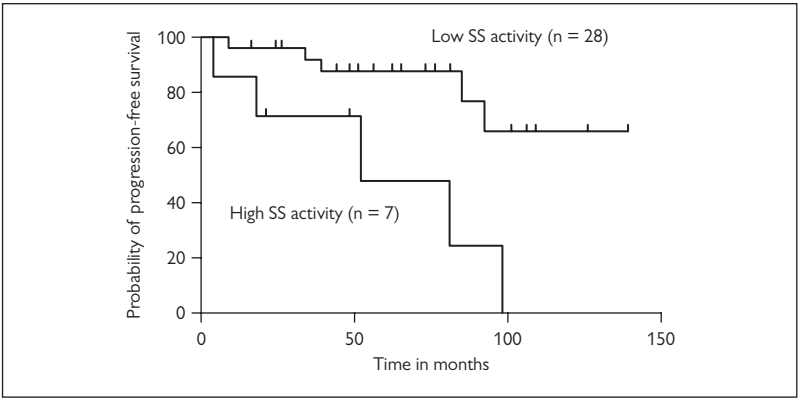

Figure 3.13 Progression-free survival of MALT lymphoma according to initial high or low SS disease activity [6].

Source: Pollard, R.P.E. et al, J Rheumatol 2011 38(10). All rights reserved.

From our experience, 'watchful waiting' seems a suitable option in patients with asymptomatic MALT lymphoma in the absence of high SS disease activity (Figure 3.12) [6], since most patients remained asymptomatic for a long period of time (Figure 3.13). In patients with symptomatic MALT lymphoma, such as a persistent disabling parotid gland swelling, but with low SS disease activity, local treatment with low-dose involved field radiotherapy to spare remaining salivary function (2x2 or 1x4 Gy) might be sufficient.

In patients with high SS disease activity, rituximab monotherapy is not sufficient for the treatment because these patients required retreatment due to the recurrence of MALT lymphoma and/or development of SS disease activity. In these patients treatment has to include more intensive immunosuppressive therapy, for instance, a combination of rituximab with cyclophosphamide and prednisone (R-CP). This combination therapy is effective in the treatment of both indolent lymphoma and autoimmune disease.

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Chapter 4

Ocular features

Saaeha Rauz

Key points

- Although SS primarily affects the lacrimal glands, other structures also contribute to the ocular surface system and may impact on the clinical presentation.
- Subjective and objective assessments are both important. Many different tools are available, some of which can be performed with specialist ophthalmological instruments or expertise.
- Severity of ocular symptoms do not always correlate with the severity of objective findings.
- Treatments should be tailored to the patient's needs, severity of dry eye, and the symptoms.
- A hierarchical treatment regime gauged upon the severity of dry eye symptoms and signs has been proposed by the dry eye workshop consisting of a combination of environmental optimization, tear supplementation, tear retention, tear stimulation, anti-inflammatories, and biological tear substitutes.

The ocular surface system

The phenotypic changes of the ocular surface and the patient's perception of ocular disease are diagnostic criteria for primary Sjögren's syndrome (pSS). The ocular surface system is a continuous epithelium with specialized anatomical areas of the cornea, conjunctiva, and lacrimal and meibomian glands, each contributing to components of, and lined by an apical matrix known as, the tear film [1]. Other contributors of the ocular surface system are the basal connective tissue matrix, the eyelashes with their associated glands, the eyelid blink mechanism, and the nasolacrimal tear drainage duct. Embedded within the ocular surface system are homeostatic processes (neural, endocrine, vascular, immune systems) that are vital for ocular surface health. The tear film is an apical mucosal matrix critical for nutrition and immunological defence. It is composed of a hydrophilic, negatively charged, heavily glycosylated glycocalyx with membrane bound and secreted mucins produced by conjunctival goblet cells that reduce surface-tension forces and increase wettability of the ocular surface. Secreted mucins intermingle with an aqueous nutritional phase produced predominantly by the lacrimal gland and support an outer lipoprotein layer derived from the meibomian glands that confer architectural stability (Figure 4.1).

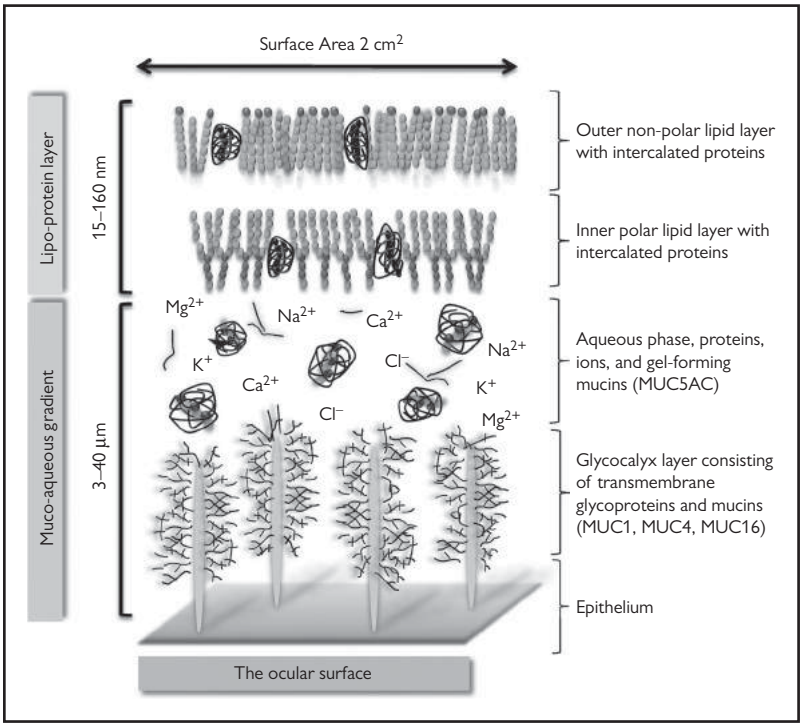


Figure 4.1 Modern schematic of the ocular surface system apical matrix 'tear film' architecture. The tear film represents an intricate apical matrix lining the ocular surface epithelial microvilli. The ocular surface epithelium is naturally hydrophobic. Wetting properties are delivered via the negatively charged transmembrane glycocalyx derived from the conjunctival goblet cells. Gel-forming mucins integrate and form a gradient within the largely lacrimal gland-derived aqueous phase. This contains nutrients (vitamins, proteins, glucose, immoglobulins, hormones, and growth factors) vital for ocular surface health. Two layers of lipids (polar and non-polar) are secreted from the eyelid meibomian glands form an outer lipoprotein coat providing stability by reducing evaporation. (Based upon a novel model proposed by the International Meibomian Gland Dysfunction Workshop 2011 and reproduced in the *Oxford Textbook of Rheumatology*, 4th edition.)

The tear film in Sjögren's syndrome

In SS, the primary pathology is an autoimmune inflammatory infiltration secondary to an unknown trigger, in response to epithelial expression of autoantigens (e.g. fodorin, SSA, SSB) of both the main lacrimal gland and the conjunctival mucosa. This results in glandular destruction and a compromised tear film associated with reduction in tear production, secretion of inflammatory mediators to the ocular surface, and altered tear composition including hyperosmolarity. Loss of ocular surface mucosal apical matrix, frictional damage from the blink mechanism, goblet cell loss, squamous metaplasia, and conjunctival scarring compounded by environmental factors (humidity, dust, heat, smoking) serve to perpetuate the pathological response. This, together with hypersensitivity of the nociceptive sensory nerves, are likely candidates for neural activation and symptomatology.

Symptoms and signs

Patients frequently complain of ocular discomfort described as dry, gritty, or burning. Severity may be mild and/or episodic elicited by environmental stressors, to severe, debilitating constant discomfort with functional implications and visual disturbance. Symptoms and signs of dry eye stratified according to disease severity are shown (Table 4.1; adapted from the report from the Dry Eye Workshop 2007). More objective symptomatology is graded through a range of patient-reported outcome tools specific to ocular surface disease such as the Ocular Surface Disease Index (OSDI) (Table 4.2) National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ25); or as part of more general scoring systems for pSS such as Profile of Fatigue and Discomfort (PROFAD), Sicca Symptoms Inventory (SSI), European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI), correlating with disease

Table 4.1 Symptoms and signs of dry eye stratified according to disease severity

Severity Level	1	2	3	4
Discomfort	Mild +/or episodic; occurs under environmental stress	Moderate episodic or chronic; stress or no stress	Severe frequent or constant without stress	Constant, severe, +/or disabling
Visual symptoms	None or episodic mild fatigue	Annoying +/or episodic; activity limiting	Annoying, chronic +/or constant; limiting activity	Constant +/or possibly disabling
Conjunctival hyperaemia	None to mild	None to mild	Mild to moderate	Moderate to marked
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Ocular surface staining	None to mild	Variable	Marked central	Severe punctate erosions
Tear film signs and impact on cornea	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis; mucus clumping; ↑ tear debris	Filamentary keratitis; mucus clumping; ↑ tear debris; ulceration
Lid, meibomian glands, and ocular surface failure*	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinisation, symblepharon
TFBUT (s)	Variable	≤10	≤5	Immediate
Schirmer's I score (mm/5 min)†	Variable	≤10	≤5	≤2

MGD= meibomian gland dysfunction; TFBUT = tear film break-up time.

Notes: * Ocular surface failure is defined as failure of mechanisms responsible for maintaining a healthy ocular surface characterized by persistent epithelial defects, keratinization of the normally non-keratinized ocular surface epithelium, and progressive conjunctival scarring with formation of symblephara (adhesions tethering the tarsal (eyelid) and bulbar (eyeball) conjunctiva).

† Schirmer's I rates are defined for strips-stimulated tear production performed without the use of topical anaesthetic.

Adapted from The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007), The Ocular Surface, Vol 5, Issue 2 (2007) 75–92.

Circle the number in Table 4.2 that best represents each answer.

Table 4.2 Ocular Surface Disease Index (OSDI)

Have you experienced any of the following *during the last week?*	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
1. Eyes that are sensitive to light?	4	3	2	1	0	
2. Eyes that feel gritty?	4	3	2	1	0	
3. Painful or sore eyes?	4	3	2	1	0	
4. Blurred vision?	4	3	2	1	0	
5. Poor vision?	4	3	2	1	0	
					Subtotal score for answers 1 to 5. **A =**	
Have the problems with your eyes limited you in performing any of the following *during the last week?*	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A
					Subtotal score for answers 6 to 9. *(If B > 10 ask subject to complete NEI_VFQ)* **B =**	
Have your eyes felt uncomfortable in any of the following situations *during the last week?*	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A
					Subtotal score for answers 10 to 12. **C =**	
Add subtotals A,B, and C to obtain D.						
Total number of questions answered (do not include questions answered N/A)						
OSDI = [(sum of scores) x 25]/(number of questions answered)						

activity or damage scores (SS Disease Activity Index (SSDAI), SS Clinical Activity Index (SSCAI), and EULAR SS Disease Activity Index (ESSDAI)).

The clinical features in pSS are described in a spectrum of staining patterns on the ocular surface using vital dyes (fluorescein, lissamine green) [2, 3] accompanied by a reduced Schirmer's test I (<5mm without anaesthetic). Other features related to dry eye disease include increased debris and mucus clumping with or without filamentary keratitis, reduced tear film breakup time, increased conjunctival inflammation, increased osmolarity, and meibomian gland dysfunction.

Dry eye severity scales are formulated by developing a hierarchy of symptoms and clinical features which together provide a putative tool to inform potential therapeutic strategies (see 'Dry eye severity and hierarchy of treatment ' in this chapter). Hyperosmolarity is now considered to be critical in guiding therapy. Nevertheless, in a sizeable subset of patients, symptomatology predominates with insignificant clinical signs. This is referred to as 'pain without stain' and is thought to be due to nociceptive sensory receptor hypersensitivity [4].

Objective assessment of dry eye

Vital staining

A number of stains are used to assess damage potentially caused by dry eye disease. Lissamine green is dose dependent and maps devitalized epithelial cells present on an intact ocular surface. Staining is persistent, so that reading of the staining pattern need not be performed directly after instillation. Visualization is enhanced by use of a white light source and a red barrier filter to give a black pattern on a red background.

Fluorescein is the most commonly used dye (2µl of 2% sterile solution) which stains epithelial defects but has the disadvantage of a blurred staining pattern if slit-lamp reading with excitation and barrier filters is delayed. It also enables measurement of tear film breakup time.

A number of scoring systems have been proposed for the ocular surface in pSS. The two commonly used staining patterns are the van Bijsterveld schema where the intensity of lissamine green score in the two exposed conjunctival zones and cornea are scored between 0–3 for each zone with a maximum score of 9 (Figure 2A) [2], and the ocular staining score (OSS) which uses lissamine green for conjunctival scoring, fluorescein for corneal scoring (0–3 each zone) with added weighting for confluent and pupillary area fluorescein staining and for the presence of filaments resulting in a maximum score of 12 (Figure 2B) [5]. A VB score of 4 equates to an OSS score of 5.

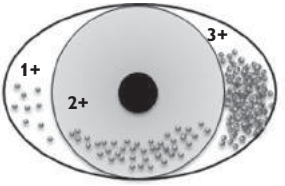
Tear film break-up time

Tear film stability is defined as the interval between the last complete blink and the first appearance of a dry spot or disruption in the tear film and is quantified as the tear film break-up time (TFBUT). After careful instillation of 5µl of non-preserved 2% sodium fluorescein onto the bulbar conjunctiva without inducing reflex tearing, the patient is instructed to blink naturally several times without squeezing to distribute the fluorescein. Within 10–30 seconds of the fluorescein instillation, the patient is asked to stare straight ahead without blinking, and using a standard slit-lamp magnification (x 10) and constant intensity background illumination on high utilizing a Wratten 12 yellow filter (≈ cobalt blue light), the duration of the tear film integrity over the cornea is observed. The TFBUT is repeated three times and the mean average is recorded. A TFBUT ≥ 10s is considered to be normal, and ≤ 5s is considered reduced.

Schirmer's test

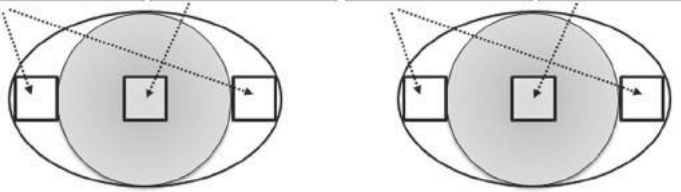
The Schirmer's test I without anaesthetic is the 'gold standard' quantitate measure of tear flow [2]. The Dry Eye Workshop (DEWS) methodology recommends insertion of filter paper strips (5 x 35mm Whatman grade No 1) bent at the notch into the conjunctival sac over the lower lid margin, midway between the middle and outer third, with the eye closed throughout the duration of the test in an *unanaesthetised* eye. The strips are read after five minutes with a cut off of ≤ 5.0mm considered to be abnormal.

(A) van Bijsterveld schema



(B) SICCA ocular staining score

Right eye				Left eye			
Conjunctiva: lissamine green		**Cornea: fluorescein**		**Conjunctiva: lissamine green**		**Cornea: fluorescein**	
Grade	Dots	Grade	Dots	Grade	Dots	Grade	Dots
0	0–9	0	0	0	0–9	0	0
1	10–32	1	1–5	1	10–32	1	1–5
2	33–100	2	6–30	2	33–100	2	6–30
3	>100	3	>30	3	>100	3	>30



Extra points: fluorescein only (mark all that apply and add to fluorescein score)		**Extra points: fluorescein only** (mark all that apply and add to fluorescein score)	
Score	Description	Score	Description
+1	Patches of confluent staining	+1	Patches of confluent staining
+1	Staining in pupillary area	+1	Staining in pupillary area
+1	One or more filaments	+1	One or more filaments

Figure 4.2 Ocular surface staining scores for pSS: (A) van Bijsterveld schema—surface damage to the exposed eye, assessed by staining Intensity scored in two exposed conjunctival zones, and cornea score 0–3 for each zone with lissamine green. Maximum score = 9. (1+ few separated spots; 2+ many separated spots; 3+ confluent spots). (B) SICCA ocular staining score: Total OSS of 3–12 per eye assesses the range of severity of keratoconjunctivitis sicca. Lissamine green is used for conjunctival scoring, fluorescein for corneal scoring (0–3 for each zone) with added weighting for confluent and pupillary area fluorescein staining and for the presence of filaments resulting in a maximum score of 12 per eye.

Schirmer's I *with anaesthetic* delivers an estimate of basal secretion, and Schirmer's II involves induction of 'reflex' secretion by irritating the nasal mucosa. Neither are routinely used for pSS dry eye disease assessment.

Tear film osmolarity

Hyperosmolarity is the driver of ocular surface dry eye vicious cycle. It is now possible to document osmoslarity in mild to moderate dry eye patients, but ability to obtain a

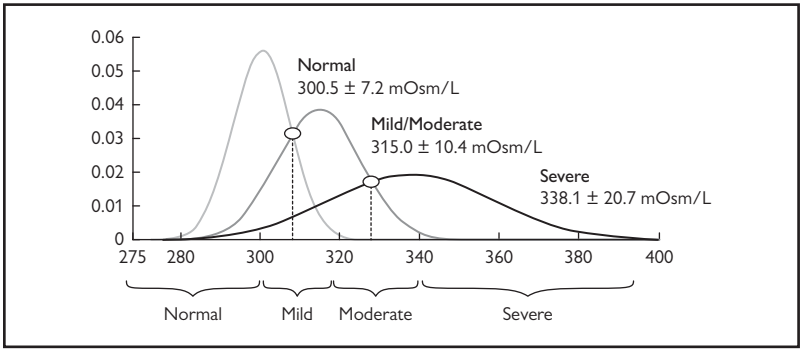


Figure 4.3 Osmolarity as a metric for the severity of dry eye disease. Osmolarity value ranges for mild, moderate, and severe dry eye disease are broad with mean of > 308 mOsm/L are generally indicative of dry eye disease. Longitudinal follow-up of patients is essential to monitor disease course as many patients fall in the normal range but have significant symptomatology, staining pattern, and severity of disease.

measurement in those with severe dry eye falls. Increased availability and affordability has enabled to use of osmolarity readings to become an integral feature of referral pathways and algorithms in primary and secondary care settings. Measuring osmolarity has a functional advantage being non-invasive, easily performed objective continuous variable and a clinical biomarker for dry eye severity [6]. Tear analysis is determined by lab-on-a-chip technology using a nanolitre collecting tool. The test cards are single use, individually packaged, and have an integral sigmoidal nanofluidic channel that collects 50nL of tear fluid by passive capillary action onto gold electrodes embedded in a polycarbonate card. This enables simultaneous collection and measurement of tear fluid direct from the ocular surface. Osmolarity value ranges for mild, moderate, and severe disease are broad with mean average of > 308 mOsm/L are generally indicative of dry eye disease (mild ≈ 308 mOsm/L, moderate ≈ 320 mOsm/L, and severe >355 mOsm/L) (Figure 4.3). Longitudinal follow-up of patients is essential to monitor changes to treatment as many patients fall in the normal range but have significant symptomatology and abnormal staining pattern.

Emerging tools

Further objective tools are on the horizon for the measurements of severity of dry eye disease. These include cytological analyses of ocular surface cells after conjunctival impression imprints followed by either (i) regular staining for examination of cellular morphology, metaplasia, keratinization, or goblet cell loss [7]; (ii) gene expression arrays; or (iii) flow cytometry of retrieved cells to identify the exact nature of infiltrated cells [8]. For example, HLA-DR is strongly expressed in cases of dry eye disease associated with ocular surface inflammation and provides a biomarker for disease activity. Other techniques include tear film proteomics or metabolomics, and ocular *in vivo* confocal microscopy.

Dry eye severity and hierarchy of treatment

Treatments should be tailored to the patient's needs, the severity of dry eye, and the symptoms. A hierarchical treatment regime gauged upon the severity of dry eye symptoms and signs has been proposed by the dry eye workshop consisting of a combination

of environmental optimization, tear supplementation, tear retention, tear stimulation, anti-inflammatories, and biological tear substitutes (Table 4.3) [9, 10].

Environmental optimization

Lifestyle, dietary, and environmental modification is fundamental to management. Strategies for removing both desiccating stress such as anti-histamines, anti-depressants, air-conditioning or dry heat, and irritating substances including cigarette smoke, pollution, or peri-ocular cosmetics, should be implemented at the outset. Avoid low humidity atmospheres such as centrally heated houses, aeroplanes, windy locations, and activities that provoke tear film instability such as prolonged reading or computer work.

The clinical benefit of omega-3 fatty acids (eicosapentaenoic acid (EPA) in fish oil) is gaining recognition due to its ability to inhibit pro-inflammatory lipid mediators (prostaglandin E2 and leukotriene B4) and block production of IL-1 and TNFα, compared to diets high in omega-6 fatty acids. In addition, clinical benefit has also been observed with linoleic acid and gamma-linolenic acid (flaxseed oil) which is metabolized to EPA before entering the anti-inflammatory cascade.

Table 4.3 Dry eye severity level and a hierarchy of treatment

Level of disease severity*	Treatment
1	*Initiate conservative treatment* • Education and environmental/dietary modifications • Elimination of offending systemic medications and preservatives • Lubricants: drops/gels/ointments • Eye lid therapy
2	*If level 1 treatments are inadequate, add:* • Anti-inflammatories • Tetracyclines for meibomian gland dysfunction • Punctal plugs • Secretagogues • Moisture chamber spectacles
3	*If level 2 treatments are inadequate, add:* • Permanent punctal occlusion • Contact lenses • Serum eye drops

4	*If level 3 treatments are inadequate, add:*
	• Systemic anti-inflammatory agents
	• Surgery
	  • Lid surgery: tarsorrhaphy
	  • Transplantation: salivary gland, amniotic membrane

Notes: *Severity level is gauged upon that defined by the report of the Dry Eye Workshop 2007 summarized in Table 4.1.

Tear supplementation

The most commonly prescribed treatment remains 'artificial tears' which function as lubricants that alleviate biomechanical trauma caused by dry eye states but do not serve to replace the intricate composition of the tear film. Elimination of older toxic preservatives such as benzalkonium chloride is critical, particularly when dosing is over four to six drops per day of the total number of eye drops being administered into the eye [11]. Although the epithelial damaging effect of preservatives is of paramount importance, their capacity to cause chronic ocular surface inflammation and paradoxical aggravation of disease is less well recognized amongst non-ophthalmological healthcare professionals. Electrolyte composition, viscosity, and osmolarity are key to synthesizing the ideal artificial tear, but incorporating nutrient properties promoting ocular surface renewal and immunological defence, currently evade commercially available pharmaceutical products and contribute to patient dissatisfaction. Lubricants containing carboxymethylcellulose maintain higher ocular surface retention and facilitate epithelial proliferation [12], whilst sodium hyaluronate glycosaminoglycans preparations deliver properties such as wound healing and reducing inflammation whilst affording long-lasting lubrication by binding CD44 molecules which are highly expressed on the inflamed ocular surface [13].

Tear retention

Promoting tear retention is maintained by a number of parameters including punctal occlusion with punctal plugs or punctal cautery, and the use of moisture chamber spectacles, contact lenses, and more invasive surgical options. Punctal plugs may be absorbable collagen or synthetic polymers that last for variable periods of time [14]. More commonly, non absorbable 'permanent' plugs consisting of either a surface collar stud resting on the punctal opening with a slimmer shaft and wider base engaging the canaliculus, or intracanalicular plugs that are concealed *in toto* within the canaliculus, are used.

Moisture chamber spectacles or goggles conserve humidity in the environment directly adjacent to the ocular surface by incorporating side panels around the spectacle rim and arms. The use of contact lenses may also help protect and hydrate the ocular surface in severe dry eyes states but should only be considered if under the direct supervision of a specialist ophthalmologist, whilst other treatments (lubrication, plugs, etc) must be upheld during the period of contact lens wear to reduce the risk of corneal neovascularization or sight-threatening corneal infection. The contact lens material is carefully chosen to allow high oxygen permeability that enables extended overnight wear and continuous use for up to three months. Alternatively, gas permeable scleral-bearing rigid contact lenses with and without fenestration may be employed. Minimizing nocturnal lagophthalmos (exposure) by taping the lids or surgical tarsorrhapy or amniotic membrane transplant to the cornea, may be required in the most severe of cases. Salivary gland autotransplantation is reserved only for severe clinical states where the mouth is not excessively dry.

Tear stimulation

Secretagogues have been used with variable success in SS dry eyes. Oral cholinergic agonists, pilocarpine, and cevilemine, reportedly improve symptoms, whereas studies have shown that pilocarpine may also increase goblet cell density in the conjunctiva [15], but use is limited by intolerable systemic cholinergic symptoms.

Anti-inflammatories

Over the last decade, targeting the inflammatory component of SS dry eyes has achieved credence. The most readily available agents are steroid based used mainly

in topical non-preserved eye drop preparations (prednisolone 0.5%, dexamethasone 0.1%) or ointments betamethasone. Ophthalmological surveillance is mandatory due to the risk of steroid-induced raised intraocular pressure which may result in permanent optic neuropathy, or cataract formation. Topical calcineurin inhibitors (ciclosporin 0.1% are licensed for use in adults with severe dry eye severe and keratitis which has not improved despite treatment with artificial tears. Topical ciclosporin has been found to improve the clinical signs of dry eye together with subjective improvement in symptoms. These agents are reported to increase goblet cell density and reduce lymphocyte activation markers, whilst sparing the local adverse effects of topical corticosteroids. Long-term tetracyclines (usually doxycycline 100 mg once daily for three months followed by 50 mg once-daily maintenance) have, in addition to their antibacterial role, anti inflammatory (anti-TNFα, IL-1), anti-angiogenic, and anti-metalloproteinase properties which are conducive to promoting an optimal ocular surface microenvironment in dry eye disease states [10].

Biological tear substitutes

The epitheliotrophic potential of serum eye drops have shown a beneficial effect in SS dry eyes due to the similarities of the large number of biological substances that are present in tears [16]. The use of blood and its components as a pharmaceutical preparation is restricted by specific national laws making widespread use prohibitive. For example, in the UK, access to autologous serum is limited through cost constraints with cost recovery obtained from GP commissioners on a named-patient basis. Allogeneic serum eye drops have recently become available for patients unable to donate their own blood (e.g. poor veins) or those whose clinical condition contraindicates blood donation.

Meibomian gland dysfunction

Patients with pSS are at higher risk of meibomian gland dysfunction (MGD) than the normal population, leading to a defective tear film lipid layer that may contribute to dry eye by excessive evaporation and exacerbating inflammation. MGD is defined as a chronic, diffuse abnormality of the meibomian glands (MG), commonly characterized by terminal duct obstruction and/or qualitative and quantitative changes in the glandular secretion [17]. Typical symptoms of eye irritation, stinging and burning with clinically apparent inflammation and ocular surface disease are recognized. The MG lie within the eyelids with their orifices behind the roots of the lashes. They represent the main source of tear film lipids that spread across the ocular surface during the blinking mechanism, but in SS dry eyes, the reservoir of lid oil may be reduced with delayed spreading. Stagnation of the oils in the glands results in an alteration of lipid structure conferring pro-inflammatory properties. This is aggravated by hyper-colonization of the lid margin by staphylococcal species that secrete esterases and lipases releasing fatty acids and mono/di- glycerides together with exotoxins giving rise to characteristic tear film 'foam'. Chronic inflammation and subsequent lid margin hyperkeratinization, cicatrization, and irreversible blockage of MG ensue.

The staging of MGD is based upon the quality of MG secretions expressed from the glands, changes in lid morphology defined by the internal migration of the muco-cutaneous junction, changes in the MG orifices, acini structure, and glandular drop out. The stage of disease is used to direct treatment protocols which include modulating diet, lid margin hygiene, warm glandular expression, topical emollient lubrication, tetracyclines, and anti-topical inflammatory therapy (Table 4.4). Effective

Table 4.4 Clinical stages of meibomian gland dysfunction with therapeutic options		
Stage of MGD	Clinical description	Treatment
1	• No symptoms • Minimally altered secretions • No ocular surface staining	• Inform patient about MGD • Alter diet, reduce environmental stress • Consider lid hygiene and warm expressions
2	• Minimal-mild symptoms of discomfort itching and photophobia • Minimal to mildly altered secretions • None or limited ocular surface staining and TFBUT < 10s	• Improve ambient humidity, increase dietary omega-3 intake • Lid hygiene and warm expression (minimum of 4 min twice daily) • Lubricants, topical azithromycin, emollient lubricant, liposomal spray • Consider tetracycline derivatives
3	• Moderate symptoms with definite limitation of activity • Moderately altered secretions with increased lid margin vascularity, telangiectasia, and orifice plugging • Mild to moderate conjunctival and peripheral corneal staining and TFBUT ≈ 5s	*All of Stage 2 treatment* • Plus oral tetracycline derivatives • Lubricant ointment • Consider anti-inflammatory therapy for dry eye
4	• Marked symptoms with definite limitation of activity • Severely altered secretions with meibomian gland drop out and displacement • Central corneal staining and conjunctival inflammation, and TFBUT ≈ 0–5	*All of stage 3 treatment* • Plus anti-inflammatory therapy for dry eye
Plus Disease	• Exacerbated inflammatory ocular surface disease • Mucosal keratinization • Phlyctenular keratitis • Trichiasis • Meibomian gland cysts • Anterior blepharitis • Demodex-related anterior blepharitis, with cylindrical dandruff	• Pulsed soft steroid as indicated • Therapeutic contact lens/scleral contact lens • Steroid therapy • Epilation, cryotherapy • Intralesional steroid or excision • Topical antibiotic or antibiotic-steroid combination • Tea tree oil scrubs

lid margin hygiene is paramount requiring application of warm compresses for up to 30 minutes twice daily to increase the fluidity of the stagnant oils within the glands which eases expression when lids are massaged by a firm stroking motion towards the lid margins. Expressed matter is cleansed lightly with a cotton tipped applicator moistened with boiled cooled water with bicarbonate, baby shampoo, or tea tree oil. Provided the disease is mild to moderate on commencing MGD treatment, lid hygiene

can improve both symptoms and clinical signs. In the presence of extensive glandular and duct atrophy associated with thickened and indurated lids, cicatrization and negligible excreta, response may only be partial or even refractory.

Uveitis

Uveitis is a rare complication of pSS characterized by bilateral or unilateral chronic intraocular inflammation where keratic precipitates (clustered cell deposits on the cornea) with or without pars plana exudates in the absence of frank chorioretinitis are typical findings [18]. Uveitis is frequently associated with an increased erythrocyte sedimentation rate (ESR), positive anti-nuclear antibody (ANA) (speckled pattern), and high titres of anti-Ro (SS-A) and anti-La (SS-B) antibodies. It may be resistant to topical steroid treatment given as eye drops. High-dose oral prednisone with or without systemic steroid-sparing agents such as intravenous cyclophosphamide and followed by long-term maintenance with oral ciclosporin may be required [19].

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Chapter 5

Fatigue, pain, and quality of life

Roald Omdal and Katrine Brække Norheim

Key points

- Chronic fatigue is one of the most disabling symptoms of primary Sjögren's syndrome (pSS).
- Fatigue is very common among pSS patients.
- There is currently no consensus on the definition of fatigue and the instruments used to measure it.
- Fatigue is a complex phenomenon with both biological and psychosocial factors.
- Management of fatigue requires a multi-disciplinary approach and should be tailored to the individual.
- pSS is also associated with musculoskeletal pain and reduced quality of life.

Fatigue

Chronic fatigue is one of the most troublesome and debilitating phenomenon that patients with primary Sjögren's syndrome (pSS) encounter. Many doctors believe that the constant feeling of dryness in the mouth and the eyes, and the muscle and joint pain are the most important complaints, but abnormal tiredness and exhaustion are regarded by many patients as the worst symptoms. Fatigue is frequently the reason for not returning to normal work and for having difficulties in daily life, even when disease activity and other features of the disease seem to be under reasonable control. There are many hypotheses and opinions about fatigue, and there is no consensus on the aetiology, pathogenesis, and treatment. It is therefore important to investigate and try to understand the mechanisms that lead to and regulate fatigue, so that relevant treatment strategies can be developed and implemented.

There is no good evidence to suggest that fatigue in pSS is different from fatigue in other diseases and conditions, and this chapter will therefore discuss fatigue as a general phenomenon, with emphasis on pSS where appropriate.

What is fatigue?

Fatigue can be defined as '… *an overwhelming sense of tiredness, lack of energy and feeling of exhaustion*' [1]. It is a common phenomenon in patients with cancer, chronic inflammatory diseases, and neurological diseases. Patients often rate fatigue as their worst complaint, the most difficult problem to cope with, and the most important reason for work disability. Fatigue is often described as a persistent lack of energy,

and does not improve after rest or sleep. As such, fatigue is fundamentally different from normal tiredness that one experiences after heavy physical work or sleep deprivation. In a qualitative study intending to capture the essence of fatigue in patients with pSS, a common pattern emerged from the descriptions of fatigue by patients was '… an ever-present, fluctuating, and uncontrollable lack of energy' [2]. This implies that in most patients the experience of fatigue is chronic, but varies in intensity, and is unpredictable and beyond control. Patients therefore have to adjust their behaviour and everyday life activities to deal with any unexpected fatigue flare ups.

When chronic fatigue occurs without any other underlying disease, the condition is sometimes referred to as chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME). Today, many researchers regard CFS as a condition of selective immunological or inflammatory disturbance in the brain, regardless of whether the precipitating factor being a viral infection or other process.

Whether patients with chronic fatigue have a well-defined underlying disease or not, fatigue is often so profound that it leads to prolonged sick leave and disablement which result in substantial economic burdens to society. Therefore fatigue should be taken seriously by clinicians, and deserves more attention from the public health authorities.

How common is fatigue?

The answer depends on which fatigue instruments and what cut-off levels are used for defining fatigue. One study suggested that about 20% of the general population scored high enough on a fatigue scale to be considered having persistent fatigue [3]. In contrast, in a French study 7.6% of patients in general practice presented to their doctor with fatigue as their major problem [4]. Estimates on how common fatigue occurs are likely to be highly dependent on the criteria applied and cut-offs used. Nevertheless, fatigue is much more frequent in patients with autoimmune and chronic inflammatory diseases (60% to 70%) [5, 6, 1], but there is no good evidence to suggest that fatigue is more severe in any disease subsets.

It has been reported that 85% of pSS patients experience fatigue, and 40% of the patients report fatigue as their most severe symptom [7] (Box 5.1). Applying the fatigue severity scale (FSS) instrument with a cut-off score ≥ 4, Segal et al found that 67% of pSS patients reported significant fatigue [8].

Are there different dimensions of fatigue?

Many people consider fatigue to have several dimensions, such as muscular (peripheral), mental (central), cognitive, motivational, and affective fatigue, among others. Such categorization is thought to reflect the observations that fatigue may specifically influence the muscles and brain, and give rise to changes in mood, etc. This assumption has led to the development of a variety of patient reported outcomes (PROMS) to measure the impact of fatigue in these different dimensions [9]. On the other hand, some people consider that fatigue is a unidimensional and global phenomenon across

Box 5.1 Epidemiology of fatigue

- Fatigue is common in autoimmune and inflammatory diseases.
- Reported prevalence of fatigue is highly dependent on which instrument is used to measure it and the cut-off level applied.
- Fatigue is experienced by 60% to 85% of pSS patients.

Box 5.2 Characteristics and impact of fatigue

- It has been suggested that fatigue has several dimensions such as physical and mental (e.g. cognitive, affective).
- Fatigue is a subjective phenomenon, and patients report that fatigue affects mood, memory, muscles, quality of life, and activities of daily living to various degrees.

all diseases and conditions [10]. As much as the voluntary muscles, mood, memory, and activities of daily living are affected (to varying degrees) in different subjects, this is a result of individual responses to or manifestations of a universal or global fatigue phenomenon. Therefore it remains under debate whether fatigue is a phenomenon that expresses itself in various dimensions or if there are several phenomena that are all regarded as 'fatigue' by patients and professionals, but represent different symptoms [11] (Box 5.2). These discordant views illustrate some of the complexities of fatigue, the challenges related to advancing our scientific understanding of fatigue, as well as the difficulties in developing effective treatments.

How to measure fatigue?

Objective markers of fatigue have not been identified. Most instruments for measuring fatigue are based on self-reported questionnaires that are filled out by the patient alone or under guidance and supervision of a healthcare professional (Box 5.3 and Table 5.1). Usually these instruments ask the patient to rate his or her fatigue severity retrospectively (for the previous few days or weeks), or to rate the impact of fatigue on activities of daily living. These instruments can be divided into the generic types that are independent of the underlying or associated disease, and the disease-specific instruments that have been constructed for use only in specific conditions or diseases. Examples of the latter include the Parkinson fatigue scale, the Bristol rheumatic arthritis fatigue multi-dimensional questionnaire (BRAF-MDQ), and the profile of fatigue for pSS. Disease-specific instruments may also incorporate some element of disease characteristics, disease activity, disease symptoms, or some impact on physical function that is believed to be a consequence of fatigue. For example, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) evaluates fatigue as well as symptoms of pain and dryness, which are frequently experienced by pSS patients [12].

Generic instruments, on the other hand, enable comparison of the severity of fatigue across different conditions. The simplest instrument is the fatigue visual analogue scale (fVAS). This is a 10-cm scale with anchor points: '*no fatigue*' and '*fatigue as bad as it can be*'. The patient draws a vertical line at a point corresponding to the severity of fatigue during the last week, and the distance from the left ('no fatigue') anchor measured in millimetres equals the fatigue score. The fVAS is an easy instrument to administer

Box 5.3 Assessment of fatigue

- Fatigue is usually measured by self-report instruments
- A variety of instruments exist, mainly categorized as generic or disease specific, uni- or multidimensional.
- Supervision by qualified personnel familiar with the instrument is necessary to ensure the questionnaire is completed correctly.

Table 5.1 Some of the most frequently used fatigue scales

Name of instrument	Author, year of publication	Dimensions	Comments
Chalder fatigue scale	Chalder et al, 1993	Multidimensional	Generic
Fatigue assessment instrument	Schwartz et al, 1993	Multidimensional	Generic
Fatigue impact scale (FIS)	Fisk et al, 1994	Multidimensional	Generic
Fatigue severity scale (FSS)	Krupp et al, 1989	Unidimensional	Generic
Multidimensional fatigue inventory (MFI-20)	Smets et al, 1995	Multidimensional	Generic
Functional assessment of chronic illness therapy—Fatigue (Facit-F)	Yellen et al, 1997	Multidimensional	Generic
Fatigue visual analogue scale (fVAS)	Wolfe, 2004	Unidimensional	Generic
Medical outcomes study short form 36 (SF-36)	Ware et al, 1983	Vitality subscale assesses fatigue	Generic health-related quality of life (HRQOL) measure
Eular Sjögren's Disease Activity Index (ESSPRI)	Seror et al, 2011	Unidimensional	Primary Sjögren's syndrome
Profile of fatigue	Bowman et al, 2004	Multidimensional	Primary Sjögren's syndrome

and has a good ability to measure response to change. However, even though it is simple, it should be filled out in the presence of a person who can explain and help. Other generic instruments such as the FSS, and the functional assessment of chronic illness therapy fatigue subscale (FACIT-F), were originally developed to assess fatigue in patients with multiple sclerosis, systemic lupus erythematosus and cancer, respectively. The latter instrument consists of 13 questions assessing the impact of fatigue on the patient's activities over the previous seven days. The medical outcomes study short form 36-item (SF-36) health survey is an instrument for measuring health-related quality of life, contains a vitality subscale to evaluate 'energy and fatigue', and has also been frequently employed in previous studies to measure fatigue.

The fVAS and FSS are unidimensional fatigue instruments. There are several fatigue instruments designed to capture various dimensions of fatigue, such as the profile of fatigue and discomfort (PROFAD), the Piper fatigue scale, the multidimensional fatigue inventory (MFI), among others. Whichever instrument is applied, it is extremely important to bear in mind that fatigue is predominantly a subjective phenomenon which is difficult to define and is poorly understood. Fatigue questionnaires should ideally be administered by qualified personnel rather than left to patients to complete without adequate supervision.

Pathogenesis of fatigue

The underpinning mechanism of fatigue is incompletely understood. Emerging evidence point to a genetic and molecular basis for fatigue, but psychological factors, pain, sleep disturbance, and dryness symptoms can also modulate the severity of fatigue.

Box 5.4 Mood disorders and fatigue

- There is a strong association between depression and fatigue.
- Commonalities between fatigue and depression instruments may introduce bias in the observed association between depression and fatigue.

Psychological factors in fatigue

Mood disorders

Several studies have shown that depression is strongly associated with fatigue (Box 5.4). It is unclear whether it is the depressive mood that exacerbates fatigue, or if there are other complex and indirect associations. In that regard, it has become increasingly clear that proinflammatory cytokines may induce depression, for example, as observed during treatment with interferon (IFN)-α for hepatitis C or some types of cancer [13]. Interestingly, fatigue is also reported as a side effect of IFN-α treatment. These observations, and others, therefore point to the possibility for some common biological pathways for depression and fatigue.

Many subjects with chronic diseases are in a certain degree of depressive mood. It is conceivable that if the disease is accompanied by severe fatigue, it will have negative impact on the mood of the sufferer. Anxiety may also affect individuals with chronic diseases, and a significant association between anxiety and fatigue has been reported. However, a recent study found depression to be more strongly associated with fatigue, whereas anxiety accounted for < 5% in variability of fatigue [14].

An inherent methodological problem concerning the well-known association between fatigue and depression is the similarities in the phrasing of the questionnaires used to measure fatigue and to evaluate mood. Such commonalities between instruments for assessing fatigue and depression may lead to bias that is often underestimated.

Learned helplessness

Some people with a chronic disease or suffering from a handicap will develop a condition characterized by an inability to cope with the challenges of the situation. These patients 'learned' to expect that nothing could be done to improve their symptoms or problems. This condition—'learned helplessness'—together with depression and pain were the three most important factors that were associated with pSS patients with fatigue in a study done in the US [8].

Sleep disturbances

Patients with conditions associated with fatigue frequently have sleep disturbances. In pSS, discomfort at night and poor sleep predicts more fatigue the next day [15].

Biological factors in fatigue

Neither age nor gender appears to be important factors determining the prevalence or the severity of fatigue, although some studies have shown that older patients have less fatigue. Anaemia and hypothyroidism are associated with fatigue. No other routine biochemical or immunological tests have been shown to be consistently predictive for fatigue.

Whether disease activity from Sjögren's syndrome contributes to fatigue remains unclear. Some studies in chronic inflammatory diseases indicate that higher disease activity is associated with more severe fatigue, although studies with contradictory data have also been reported.

Box 5.5 Biological factors in fatigue

- Sickness behaviour, characterized by sleepiness, social withdrawal, and loss of appetite, is observed in animals during inflammation.
- Fatigue in humans can be considered a form of sickness behavior.
- The pro-inflammatory cytokine IL-1 plays a pivotal role in inducing sickness behaviour.
- Certain SNPs have been reported to be associated with fatigue in breast cancer, CFS/ME, and pSS.

What are the possible explanations for the uncoupling between disease activity and fatigue if the latter is mediated by inflammation (Box 5.5)? Activation of the immune system not only induces production of pro-inflammatory cytokines, but also biological changes that counter-regulate the immune response, as well as protective molecules to defend against the danger of inflammation such as oxidative stress to healthy cells. It is likely that adaptive and evolutionarily conserved behavioural responses are being regulated at least to some degree through these systems.

A model for understanding fatigue is the '*sickness behaviour model*' in animals. Sickness behaviour is a survival-enhancing strategy, observed during infection and inflammation, and is highly conserved during evolution. It is characterized by sleepiness, social withdrawal, and loss of appetite, and is a complex and automated behaviour believed to protect the sick individual from predators [16]. Sickness behaviour has many features resembling fatigue.

Activation of innate immunity cells leads to production of pro-inflammatory cytokines such as interleukin (IL)-1β. This cytokine is passively and actively transported through the blood-brain barrier, resulting in sickness behaviour through the activation of specific receptor complexes on neurons in the brain.

Fatigue in humans can be considered a manifestation of sickness behaviour, and observations in humans confirm several findings from animal studies. For instance, studies in pSS show that the IL-1 system is activated in the cerebrospinal fluid and that blocking of IL-1 with an IL-1 receptor antagonist ameliorates fatigue in pSS [17]. These observations strengthen the view that the IL-1 system plays a significant role in fatigue.

Many other theories have been proposed about the cause of 'lack of energy' that is experienced by people with fatigue. Mitochondrial dysfunction, disturbances of the hypothalamic-pituitary-adrenal axis, and neuroendocrine disorders have all been implicated, but with inconsistent results in different studies. Autonomic dysfunction seems to play a role in fatigue manifestation [18].

Genes and fatigue

How can we explain that in specific diseases fatigue differs in intensity between individuals, having seemingly the same levels of disease severity or activity? It is likely that variation in the genetic background, such as single nucleotide polymorphisms (SNPs), known to influence a person's susceptibility to disease, may also influence the level of fatigue [19, 20]. This may be due to altered activity in the signalling pathways that regulate fatigue. Genetic variants involved in inflammation and immune responses have also been reported to be linked to fatigue. For instance, SNPs in genes coding for cytokines TNF-α and IFN-γ had been reported to be associated with CFS [21], as was a SNP in the promoter region of IL-6 in breast cancer survivors [22]. Genes related to oxidative stress and mitochondria functions are also of interest, and our group has reported an association between fatigue and an SNP in the gene SLC25A40, which encodes a mitochondrial protein [23].

Box 5.6 Fatigue in pSS

- Fatigue in pSS is influenced by depression, pain, sleep, and autonomic dysfunction.
- Sickness behaviour, induced by pro-inflammatory cytokines, could be a helpful framework for understanding fatigue in pSS.

Fatigue in pSS

The reported prevalence of fatigue in pSS is 60% to 85%, depending on the fatigue-measuring instrument used and the cohort investigated. There is no consistent association between fatigue and disease activity as measured by 'inflammatory markers' such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Furthermore, antibody status, such as the presence of anti-SSA antibodies, is not associated with fatigue. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) has recently been developed for pSS. The relationship between ESSDAI and fatigue has not yet been reported.

There is evidence indicating that fatigue in pSS may be caused by mechanisms similar to that underpinning sickness behaviour, in particularly the IL-1 system [24, 17]. Interestingly, white matter hyper-intensities (WMH) lesions in the brain, as detected by MRI, are non-specific findings that may reflect distortion of the blood-brain barrier, are associated with fatigue in pSS [25]. In addition, pain, depression, sleep disorders, and autonomic dysfunction may also contribute to fatigue in pSS [18] (Box 5.6).

Management of fatigue

No drug has been approved for the treatment of fatigue in pSS and there is no published management guideline available. We recommend a systematic approach to the management of fatigue in pSS (Box 5.7). Firstly, factors that may contribute to fatigue such as anaemia, hypothyroidism, and depression should be identified and treated. Many patients may benefit from cognitive behavioural therapy (CBT), often in conjunction with other treatments. Patients with learned helplessness are most likely to respond to CBT. Aerobic training has been consistently reported to improve fatigue across different conditions, including pSS. However, in our experience it is very difficult for patients with fatigue to maintain regular training over time; group based exercise may reduce the drop-out rate.

Hydroxychloroquine is frequently prescribed to patients with pSS. There are many anecdotal clinical observations of pSS patients with fatigue benefited from hydroxychloroquine. However, in a recent study, hydorxychloroquine was not superior to placebo in improving symptoms of fatigue in pSS [26]. Biological drugs have been reported to alleviate fatigue in different chronic inflammatory diseases. Rituximab, a B-cell depleting agent, has been reported to reduce fatigue in pSS [27], while data for using abatacept and belimumab in ameliorating fatigue in pSS are awaited.

Box 5.7 Management of fatigue

- Fatigue can be treated and should be tailored to individuals.
- Treatment of contributing factors such as anaemia, hypothyroidism, and depression, is important.
- Hydroxychloroquine may benefit some pSS patients with fatigue.
- Biological drugs may also be beneficial.

Pain

Pain is a common feature in pSS. Most patients report musculoskeletal and joint pain, the latter usually in a migratory pattern. The origin of the pain is unclear, however, a recent study states that neuropathic pain is the most common, followed by nociceptive pain [28]. Inflammatory arthritis is a recognized systemic manifestation of pSS but overt synovitis is uncommon. Several studies have investigated the presence of subclinical synovitis using ultrasound and has found a significant proportion of pSS patients may have mild changes such as synovial thickening or grade I Doppler signals, but the relationships between such ultrasound changes and symptoms is not clear. Myositis also occurs in pSS but is uncommon and is unlikely to be the cause of musculoskeletal pain in the majority of pSS patients. Fibromyalgic type pain may affect up to 20% of pSS patients. Pain is often associated with fatigue and depression, but the precise relationship between these factors is not clear. Treatment is largely symptomatic except in those with objective inflammatory changes in the joints, muscles, or nerves.

Quality of life

SS-specific quality of life (QoL) measurement tools have not been developed. However, QoL has been reportedly reduced in pSS using various different generic instruments, and even more so in patients with fatigue [7, 29]. QoL correlates with symptoms of dryness, fatigue, and pain, as measured by the ESSPRI, as well as with disease activity, as evaluated by ESSDAI. Other factors known to influence QoL are social support, concomitant depression, and ability to cope with chronic illness. Mood should be evaluated, and depression, if present, should be treated. A recent study investigating sexual QoL in women with pSS as compared to healthy women found a significant negative impact by pSS [30]. Patient education and information on pSS is important, and may give the patient a feeling of control and predictability in everyday life.

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Chapter 6

Systemic (extra-glandular) features

Elizabeth Price

Key points

- Systemic (extra-glandular) features affect 70% of patients with primary Sjögren's syndrome (pSS).
- They are severe in 15% of cases.
- Systemic features are more common in those with anti-Ro/La antibodies.
- The most commonly involved organs are joints, lungs, skin, and peripheral nerves.
- Hydroxychloroquine may improve the outcomes in patients with systemic features.
- Anti-B-cell therapies have shown promise and newer treatments are in development.

Introduction

Systemic (extra-glandular) features affect 70% of patients with primary Sjögren's syndrome (pSS), are severe in 15%, and are more common in patients with anti-Ro/La antibodies. The most commonly involved organs are joints, lungs, skin, and peripheral nerves.

Fatigue

Physical and mental fatigue are reported by at least 75% of patients with pSS, and for many, are the most disabling symptoms (see also Chapter 5). Higher levels of psychological distress are found in pSS patients compared to healthy controls and certain personality features (negativity, preoccupation with detail, perfectionism, and anxiety) are more prevalent in patients with pSS.

Constitutional symptoms

These are most common in the anti-Ro/La antibody positive group:

- Lymphadenopathy is reported in up to 30% of pSS patients.
- A low grade fever can be present at times of disease flare.
- Some patients experience weight loss.

Lymphoma

(See also Chapter 8.)

- Risk of lymphoma increases from 3% in the first five years to 9.8% after 15 years i.e. up to 40 times the population risk.
- The majority are of the mucosa-associated lymphoid tissue (MALT) type.
- The median age of onset is mid-50s and the diagnosis of pSS generally pre-dates the lymphoma by a mean of seven years.
- Predictive factors for later development of lymphoma include anti-Ro/La positivity, leucopaenia, lymphadenopathy, recurrent/persistent salivary gland swelling, and reduced C4 levels.
- The commonest sites of presentation include the parotid and other salivary glands, followed by the orbits, stomach, thyroid, lung, and upper airways. Rarely other sites are involved.
- Presentation is usually with a firm, palpable swelling within the gland.
- Gastrointestinal tract lymphoma may present with chronic diarrhoea, malabsorption, and weight loss.
- Biopsy is necessary to confirm the diagnosis.
- Computer tomography (CT) scanning is helpful for staging.
- Treatment is generally with surgical excision followed by radiotherapy, chemotherapy, or a combination of the two.
- The prognosis is generally good with a complete response to initial treatment in > 90% and five-year disease-free survival > 75%.

Practical tips

Painful, salivary gland swelling is common in primary SS (pSS). Warn patients to report firm, painless swelling that does not settle. Investigate with ultrasound, magnetic resonance imaging (MRI), biopsy, and CT chest, abdomen, and pelvis for screening/staging.

Musculoskeletal

- Joint symptoms are a presenting feature in a third of pSS patients and occur during the course of the disease in over half of patients.
- The arthritis is predominantly peripheral, symmetrical, polyarticular, and intermittent. Usually non-deforming, non-erosive, and synovitis is generally mild and may be sub-clinical but detectable on ultrasonography.
- Metacarpophalangeal (MCP), proximal interphalangeal (PIP) joints and wrists are the most commonly affected.

Cutaneous

- Dry skin affects at least 50% of pSS patients and can cause pruritis. Treatment is with simple moisturisers and the avoidance of perfumed products.
- Hypergammaglobulinaemic purpura (HGP) affects about 9% of patients and causes a non-palpable purpura, usually on the lower legs. It is associated with anti-Ro/La positivity and high serum immunoglobulin levels, and histological examination demonstrates

Box 6.1 The Amsler test grid

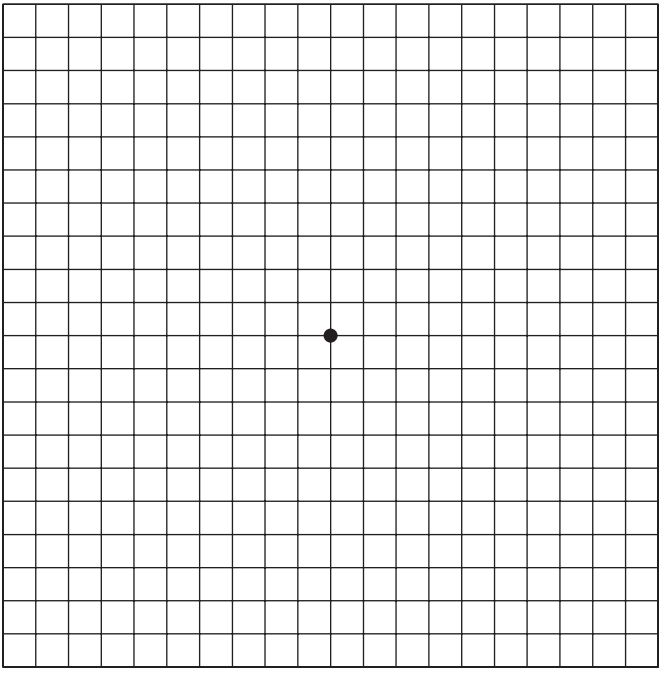
Use this Amsler grid to check your vision on a regular basis.

If you need reading glasses, please wear them. The grid should be roughly the same distance from your eyes as regular reading material.

Cover one eye, then focus on the dot in the centre.

- Do any of the lines look **wavy, blurred, or distorted**? (All lines should be straight, all intersections should form right angles, and all the squares should be the same size.)
- Are there any **missing areas or dark areas** in the grid?
- Can you **see all corners** and sides of the grid?
- Don't forget to **test both eyes**.

VERY IMPORTANT: Report any irregularity to your doctor immediately.



immunoglobulin and complement in the vessel walls of involved skin suggesting immune complex deposition. It often responds to treatment with hydroxychloroquine which lowers serum immunoglobulin levels.

- Sub acute cutaneous lupus (SCLE) appears as a photosensitive, non-scarring rash, usually on the face, arms, and front of the chest. It is more common among pSS patients with anti-Ro/La antibodies. Treatment includes sun avoidance, the use of a high factor sunscreen, and hydroxychloroquine. Mepacrine or chloroquine may also be effective. For some patients, additional immunosuppressive drugs such as azathioprine, methotrexate, and thalidomide are required.

- Less frequent skin manifestations include annular erythema, which is more commonly seen in anti-Ro/La positive Asian SS patients, granulomatous panniculitis, urticarial vaculitis, and cutaneous lymphoma.

Practical tips

Joint and skin involvement are common. Consider treatment with hydroxychloroquine 200 mg twice daily, reducing to 200 mg daily over the longer term. Warn patients about the need for annual eye testing and that onset of action may take longer than six months. Suggest self-testing with amsler chart (see Box 6.1) to detect early retinal involvement.

Raynaud's phenomenon

Raynaud's phenomenon affects 13% to 80% of patients with pSS in different series. It may precede the sicca symptoms in 42% of patients. Known precipitants such as smoking and beta-blockers should be avoided. Pharmacological treatments include calcium antagonists (e.g. nifedipine, amlodipine) and angiotensin converting enzyme (ACE) inhibitors, although side effects of these treatments may limit their use.

Practical tips

Raynaud's phenomenon is common but usually mild. Suggest practical measures and ginkgo biloba before trying drug treatments.

Pulmonary

- A chronic cough related to drying of the mucous membranes is common. Treatment with pilocarpine can stimulate secretions and reduce symptoms.
- Carbocisteine reduces sputum viscosity and may provide some symptomatic relief.
- Poor correlation between symptoms, clinical signs, and radiological findings.
- Serositis, similar to that seen in systemic lupus erythematosus (SLE), occurs occasionally. It responds promptly to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids.
- Plain radiograph abnormalities can be detected in 14% of patients (the most common finding is fine reticular changes affecting the lower lobes).
- CT scan abnormalities are present in 34% of patients (the most common findings are parenchymal linear opacities and bronchiolar abnormalities).
- Only 26% with radiographic changes are symptomatic.
- Occasionally patients present acutely with lymphocytic interstitial pneumonitis (LIP). Clinical manifestations include fever, cough, and dyspnoea, with bibasilar pulmonary infiltrates consisting of dense interstitial accumulations of lymphocytes and plasma cells. LIP usually responds well to treatment with steroids and the main differential diagnoses are pulmonary lymphoma and pneumocystis pneumonia.
- There are anecdotal reports of patients presenting with severe pulmonary hypertension, but this is rare and usually affects patients with anti-Ro/La antibodies. Echocardiographic evidence of predominantly mild pulmonary hypertension may be detected in 15% of patients and correlates serologically with hypocomplementaemia and cryoglobulinaemia and clinically with easy fatigability.

Practical tips

Persistent dry cough is common and irritating. Try pilocarpine 5 mg once daily increasing at weekly intervals to 5 mg ter die sumendum (TDS) (three times per day). Carbocisteine reduces viscosity of secretions and helps some patients. If the patient has basal crackles, consider chest radiography, CT scanning, and lung function testing.

Neurological

- Diffuse sensorimotor neuropathy, confirmed on nerve conduction testing, affects 13% to 25% of patients. Presents insidiously and only slowly progressive. Not improved by steroids or cyclophosphamide, but progress may be slowed with hydroxychloroquine.
- Trigeminal neuropathy/neuralgia has been described in up to 5% of patients with pSS. It does not usually respond to treatment with steroids and in general is treated as for trigeminal neuralgia of unknown cause. If it is felt to be related to pSS then hydroxychloroquine may be helpful as it has been shown to reduce underlying disease activity in some patients [1].
- Mononeuritis multiplex is probably seen in less than 3% of pSS patients over their lifetime. The commonest nerve affected is the lateral popliteal and this may result in a foot drop. Other affected nerves include the median, ulnar, radial, and sciatic nerve. It is associated with vasculitis and may respond to treatment with steroids and cyclophosphamide.
- Dorsal root ganglionitis is uncommon. It can cause a severe sensory neuropathy with ataxia, an autonomic neuropathy (with a rapid pulse rate, severe dizziness on standing), and trigeminal neuropathy. In half of the cases it does not progress and because of its rarity, experience with treatments is limited.
- Autonomic neuropathy can cause a multitude of symptoms including postural hypotension, nocturnal diarrhoea, urinary retention, sweating, and dizziness, and may be under-recognized in pSS. There is conflicting data on its prevalence:it was not seen at all in one study; affected 3% in a neurological case series; 70% in a series focusing on gastrointestinal and urological features; and there are numerous case reports in the literature. It is usually mild and often does not require any specific treatment. If dizziness on standing is a problem, then support stockings may be helpful and fluid retaining drugs are sometimes used.
- Myelopathy may affect up to 3% of pSS patients and can mimic multiple sclerosis. Patients present with paraplegia, sensory changes, and bladder dysfunction. Diagnosis requires MRI scanning, which shows white matter lesions, and lumbar puncture, which shows a mild elevation of cerebrospinal fluid (CSF) protein and matched oligoclonal bands in CSF and serum. Steroids and cyclophosphamide may be helpful.
- Signal hyperintensities on brain MRI have been described in patients with pSS and have been postulated to indicate the presence of an underlying cerebral vasculopathy. Correlation with serological abnormalities and clinical symptoms is poor, however, and response to treatment has not been reliably reported.

Practical tips

Hydroxychloroquine may slow progress or prevent deterioration of neurological symptoms. Small fibre neuropathy may be missed on nerve conduction studies but can be detected on biopsy. Consider specialist centre referral if concerned.

Renal

Significant renal disease is rare.

- Mild abnormalities of kidney function in about 50%.
- Mild proteinuria (1.5–0.42 g/24 h) is common (44%) but almost always asymptomatic.
- Distal renal tubular acidosis (RTA) is found in up to 33% of patients but is generally mild and often requires no treatment or simple measures such as bicarbonate to restore the urine pH.

Overall 27% of pSS patients report increased urinary frequency and 36% complain of suprapubic pain. The frequency of urinary tract infection (UTI) in patients with pSS is generally higher than expected in the general population.

Interstitial cystitis causes chronic inflammation of the bladder wall in the absence of infection and is often seen in association with connective tissue disease. 90% of sufferers are female. Anecdotal reports suggest that it is common in pSS. Both anti-histamines and cimetidine, which act as a mast cell stabilizer, have been used to treat the symptoms. Steroids and ciclosporin have been used to treat the underlying disease. Some urologists use bladder instillations of dimethyl sulphoxide (Rimson-50) or sodium hyaluronate.

Practical tips

It is very rare to get clinically significant or progressive renal disease. Dysuria can interfere with quality of life and cimetidine is worth a try.

Haematological

Haematological abnormalities are common, but generally mild and asymptomatic:

- Leucopaenia occurs in 14% to 42% of patients.
- Normochromic, normocytic anaemia in up to 11%.
- Thrombocytopenia in 5% to 15%.
- Autoimmune haemolytic anaemia (AIHA) is relatively rare.

In many cases, no treatment is required but the haematological abnormalities usually respond to treatment with steroids and in refractory cases, rituximab has been helpful.

Practical tips

Short courses of oral steroids may help if clinically significant. If counts fall on steroid withdrawal then it may be worth trying azathioprine or mycophenolate. If this fails, then rituximab is often effective.

Thyroid disease

Accompanying thyroid disease is seen in up to 20% of patients [2]. Thyroid autoantibodies are present in 20% to 30% of patients. Treatment is with thyroxine replacement or anti-thyroid drugs, as appropriate.

Gastrointestinal and hepatic

- Irritable bowel syndrome (IBS)-like symptoms are common.
- There are antibodies to tissue transglutaminase (TTG) in 12% of patients.
- Coeliac disease appears in up to 4.5%.
- Mild abnormalities of liver enzymes in 7%.
- Primary biliary cirrhosis (PBC) with PBC-associated autoantibodies found in about 6%.
- Mild elevation of pancreatic enzymes is not uncommon but more serious problems occur in no more than 1% of patients.

Practical tips

IBS symptoms may be helped with treatment with bulking agents and anti-spasmodics. Treatment of PBC is usually with ursodeoxycholic acid which can slow the progress of the liver condition and improve the long-term outlook.

Immunological

Hypocomplementaemia is seen in a subgroup of patients and is associated with a higher frequency of vasculitis, lymphoma, leucopaenia, and cryoglobulinaemia. It is an independent risk factor for the development of lymphoma. Hypergammaglobulinaema is found in the majority of the anti-Ro/La positive group and is strongly associated with extra-glandular manifestations. A low positive dsDNA antibody has been described in a small proportion (< 5%) of the anti-Ro/La-positive patients.

Practical tip

Hydroxychloroquine can be very effective in lowering the hypergammaglobulinaemia over time and may prevent development of further complications.

Vaginal

- Vaginal dryness affects 76% of patients.
- Dyspareunia affects 40%.
- Recurrent candida infection is common.

Practical tips

Simple lubricating gels can aid intercourse. Use longer-acting non-hormonal vaginal moisturisers to improve moisture levels within the vagina (several are all available over the counter from pharmacies). Oestrogen-containing creams can improve the quality of the genital skin, are safer than oral hormone replacement therapy, and can be used in combination with the non-hormonal moisturisers. Oral pilocarpine can also improve vaginal secretions.

Pregnancy

- Fertility is unaffected by pSS.
- Small increased risk of recurrent miscarriage in the anti-Ro/La positive group.

- Neonatal lupus rash occurs in about 5% of live births in anti-Ro/La positive women, which usually appears at six weeks of age and lasts about 17 weeks before fading and clearing completely. A few children have persistent depigmentation or telangiectasia.
- Congenital heart block (CHB) occurs in less than 2% of pregnancies in women with anti-Ro/La antibodies and may be detected by ultrasound scanning from about 16 weeks gestation. Of affected children, 70% survive, but nearly all require pacemakers in the first few months of life. The risk is higher among those with anti-Ro52 antibodies.
- Following an affected pregnancy the risk of CHB goes up to 17% for subsequent pregnancies.
- Other, very rare, complications include hepatitis and cytopenias affecting the newborn. Only a handful of cases have been reported in the literature and in the majority of cases the child has improved spontaneously.

Practical tip

Successful pregnancies are increasingly common in patients with pSS. Consider low dose aspirin to improve placental implantation and monitor closely with serial ultrasound scan. It is safe to continue hydroxychloroquine throughout pregnancy.

Systemic treatments

Hydroxychloroquine is the most commonly prescribed systemic treatment. Studies have demonstrated a fall in erythrocyte sedimentation rate (ESR) and immunoglobulin levels but no change in tear or salivary flow. Fatigue, the most common systemic symptom, was not assessed in the historical studies but a more recent study showed an improvement in fatigue after 12 months of treatment and anecdotal reports support this.

To date other conventional systemic treatments have proved disappointing. Prednisolone has not been shown to be of consistent benefit for either the glandular or extra-glandular manifestations. Low dose azathioprine, ciclosporin, methotrexate, leflunomide, and mycophenolate have all been trialled in studies with modest benefit and significant side effects. However, steroids and other immunomodulators can be helpful in selected patients in certain situations. Trials evaluating anti-tumour necrosis factor (TNF) agents found no benefit in systemic symptoms. Rituximab has shown some improvement in extra-glandular features in studies to date. A recent randomized controlled study did not demonstrate overall benefit to primary outcome at 24 weeks, but post-hoc analysis suggest benefits to various clinical parameters at earlier time points. Abatacept and belimumab have shown some promising data in small open label trials and newer biologics and targeted small molecules are in development.

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Chapter 7

Evidence-based evaluation and therapies

Raphaèle Seror and Divi Cornec

Key points

- The European League Against Rheumatism EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is a standardized outcome tool for the assessment of systemic disease activity of primary Sjögren's syndrome (pSS) patients.
- The EULAR Sjögren's syndrome patient reported index (ESSPRI) is a standardized tool for the evaluation of patient-reported outcomes in pSS.
- There are currently very few evidence-based therapies available for pSS.
- Several biological therapies, including those targeting novel pathways or molecules, are currently being evaluated.
- The most appropriate primary end-point for the clinical trials in pSS remains to be determined, but data from ongoing and future trials should be informative.

Introduction to evidence-based evaluation and therapies in primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a systemic disorder mainly characterized by lymphocytic infiltration of exocrine glands, resulting in functional impairment of salivary and lachrymal glands. But the inflammatory process extends beyond the exocrine glands and may result in systemic manifestations such as synovitis and vasculitis, and skin, lung, renal, and neurological involvement. These manifestations are the consequence of chronic B-cell activation, which is also responsible for an increased risk of lymphoma development [1]. As a result, clinical features might be divided into two facets: (i) benign but disabling patients' symptoms such as dryness, pain, and fatigue that affect almost all patients; and (ii) systemic, potentially severe, manifestations that may affect 70% of patients.

However, during the past decade, clinical trials and evidence-based therapy for SS were largely limited to the treatment of sicca features [2, 3, 4, 5], or patient-centred composite criteria [6, 7]. Thanks to the emergence of promising treatment such as B-cell-targeted therapies, the European League Against Rheumatism (EULAR) SS task force has set up a collaborative project to develop consensual outcome measures. Two outcome measures have been developed: the EULAR Sjögren's Syndrome

Patient Reported Index (ESSPRI) for patients' symptoms [8] and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) for systemic features [9, 10].

The purpose of this chapter is to address the evidence-based evaluation that has emerged in pSS, thanks to the newly designed clinical trial and the use of EULAR scores, which will help assess the effect of new targeted therapies.

Consensus EULAR SS indexes

Assessment of systemic disease activity: The ESSDAI

The ESSDAI is a systemic disease activity index that was developed in 2009 by consensus by a large group of experts from around the world, including Europe and North America [9]. The ESSDAI covers 12 domains of organ systems: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system (PNS), central nervous system (CNS), haematological, glandular, constitutional, lymphadenopathy, biological. Each domain is divided into three to four levels, depending on their degree of activity (Appendix 1a). Each domain is weighted according to its severity. ESSDAI is designed to measure disease activity and avoid rating of damage. The score of each domain is the level of activity multiplied by the domain weight. The final score—the sum of all domain scores—falls between 0 and, theoretically, 123, with 0 indicating no disease activity. ESSDAI has been shown to be extremely reliable, and has high and accurate sensitivity to detect any changes, thus determine any improvement [11, 12]. As disease activity measures, ESSDAI has been shown to be correlated with B-cell biomarkers of disease activity [13, 14], and predictors of lymphoma development [15, 16].

To help both physicians and researchers, disease activity levels and minimal clinically important improvement (MCII) have been determined using ESSDAI [17]. Thus low, moderate, and high activity levels were defined by an ESSDAI < 5, between 5 and 13, and ≥ 14, respectively. Also, MCII in ESSDAI has been defined as an overall improvement in ESSDAI by at least three points.

Assessment of patients' symptoms: The ESSPRI

The ESSPRI was developed in 2011 by a multicentred international cohort of 230 patients [18]. The selection of domains was based on previous data, including patient interviews [18, 19], and comprised of dryness, pain, and fatigue. The ESSPRI uses 0 to 10 numerical scales, one for each domain (Appendix 1b). The weight of the domains is identical, and the final score is the mean score of the three domains. ESSPRI has been shown to be extremely reliable, but has lower sensitivity to change than ESSDAI [12].

As in the case of ESSDAI, relevant thresholds have been determined with ESSPRI [17]. Thus, the patient satisfactory symptom state (PASS) has been defined as ESSPRI <5 and MCII as an improvement over ESSPRI of at least one point, or 15%.

Use of EULAR scores

ESSDAI and ESSPRI have now been used and evaluated in a large number of studies. ESSDAI's high sensitivity to change has been confirmed in independent cohorts of patients treated by rituximab in clinical trials [20, 21], where ESSPRI had also a good, but lower sensitivity to change. Another important point is that ESSPRI and ESSDAI have been found to be poorly correlated in different studies [22, 23, 24], which suggests that patients' symptoms and systemic complications are two different components, that

should both be evaluated, but separately. These tools are now used as entry criteria and the primary outcome of most of the recent and ongoing trials.

An alternative data-driven criterion has been recently suggested from a post-hoc analysis of the TEARS trial (evaluating the efficacy of rituximab) [25]. Five sensitive-to-change items were selected (oral dryness VAS, ocular dryness VAS, fatigue VAS, unstimulated whole salivary flow, and erythrocyte sedimentation rate), and the Sjögren's Syndrome Response Index (SSRI)-30 response was defined as an at least 30% improvement from baseline of at least two among these five items. Nevertheless, the potential of this index to evaluate the effect of B-cell and other targeted therapies needs to be further evaluated.

The objective is now for these indexes to be used as outcome criteria in a randomized controlled trial (RCT), in order to be able to demonstrate, if any, efficacy of treatments. Effectively, the treatment of pSS remains a challenge, since most RCTs, even the most recent ones, failed to demonstrate efficacy of the evaluated treatment.

Evidence-based therapy

Until now, the treatment of pSS mostly relies on symptomatic agents to relieve the main symptoms (tears and saliva substitutes, saliva stimulating agents such as pilocarpine or cevimeline, and analgesics) and steroids with immunosuppressants in case of severe systemic involvement, but the scientific evidence is scarce [26]. Topical ocular 0.05% cyclosporine led to significant improvement in the Schirmer's test and corneal staining scores in an RCT in patients with dry eyes of various etiologies [27], but has no effect on other symptoms. After the failure of anti-TNF agents (infliximab or etanercept) to demonstrate their efficacy in randomized control trials [6, 7], great hope was generated by biological therapies like in other systemic autoimmune diseases such as rheumatoid arthritis. Despite promising efficacy data of different biologic treatments in open-labelled studies (Table 7.1), most randomized controlled studies have been negative until now (Table 7.2).

B-cell targeted therapies

Growing evidence that the B-cell activating factor (BAFF or B lymphocyte stimulator) [28] and B cells play a leading role in the disease [29] justified targeting this pathway in the treatment of pSS.

Rituximab

Registries and open-labelled studies: rituximab is a chimeric monoclonal antibody targeting CD20, a B-cell-specific membrane protein, which acts through depletion of mature B cells for four to twelve months. Several open-labeled studies with sample size of 15 to 30 patients have been conducted to evaluate the efficacy of rituximab in pSS patients [30, 31, 32, 33]. Some of these studies reported an improvement in the main pSS symptoms (fatigue, dryness, and pain) and the quality of life [34] in the six months following the infusions. A longer follow-up suggested that this clinical efficacy was transient [35]. A recent study reported the effects of a much longer and intense exposure to rituximab (five courses over two and a half years), and suggested that repeated courses could have a prolonged efficacy [36].

Other studies reported that rituximab induced a clinically significant improvement in the vast majority of patients with low-grade lymphoma [31] or systemic inflammatory manifestations [37]. Analysis of France's nationwide 'AutoImmunité et Rituximab'

Table 7.1 Published open-labelled studies of biological therapies on pSS

Reference	Treatment and type of study	Number of participants	Primary end-point
Steinfeld et al 2001	Infliximab	16	Weeks 2, 6, 10, or 14: Relapse defined as a 30% increase in symptoms of dry eyes, dry mouth, or fatigue, and/or a 30% increase in the ESR
Zandbelt et al 2004	Etanercept	15	Weeks 4, 8, 12, 18, and 24: MFI questionnaire, VAS, serological monitoring, salivary flow tests, Schirmer's test, Rose Bengal corneal stain, tear-film breakup, SGB
Pijpe et al 2005	Rituximab	15	Weeks 5 and 12: Immunologic markers, salivary/lacrimal functions, and subjective parameters. MALT-type lymphoma was restaged 12 weeks after treatment initiation in the MALT/primary SS group.
Steinfeld et al 2006	Epratuzumab	16	Improvement ≥ 20% in at least two of four parameters: Schirmer's test, unstimulated whole salivary flow, VAS for fatigue, and ESR, ±IgG level
Devauchelle-Pensec et al 2007	Rituximab	16	Weeks 12, 24, and 36: Safety and clinical and biological parameters, SGB, SF-36 and SGUS
Mariette et al 2015 BELISS	Belimumab	30	Week 28: ≥ 30% reduction of two of five response criteria: patient dryness, fatigue, musculoskeletal pain VAS, physician systemic activity VAS, serum levels of B-cell activation biomarkers (25%)
St.Clair et al 2013	Rituximab	12	Week 26: Safety and clinical and biologic activity
Meiners et al 2014	Abatacept	15	Weeks 4, 12, and 24 (on treatment): ESSDAI and ESSPRI at weeks 36 and 48

ESR = erythrocyte sedimentation rate; MALT = mucosa associated lymphoid tissue; MFI = multidimensional fatigue inventory; SGB = salivary gland biopsy; SGUS = salivary gland ultrasound; VAS = visual analogic scales.

(AIR) registry reported that rituximab treatment improved systemic manifestations of the disease in 69% of the patients and allowed a decrease of steroid use [38], especially in case of peripheral nerve involvement associated with cryoglobuliemia or vasculitis [39] and for patients with central nervous system manifestations [40]. Of note, many of these patients had a severe presentation, and probably could not have been included in a placebo-controlled trial due to the risk of organ damage or even fatal issue. Thus, these data support the efficacy of rituximab in the systemic inflammatory manifestations of pSS.

Randomized controlled studies: To confirm these findings, four randomized controlled studies have been conducted. The first published trial, performed in the UK,

Table 7.2 Randomized controlled studies of biologicals in pSS

Reference	Treatment	N	Primary end-point	Significant difference for primary end-point
Sankar et al 2004	Etanercept	14	≥ 20% improvement from baseline for two of three domains: subjective or objective measures of dry mouth and dry eyes, and IgG level or ESR	No
Mariette et al 2004 TRIPPS	Infliximab	103	Week 10: ≥ 30% improvement in two of three VASs measuring joint pain, fatigue, and the most disturbing dryness	No; no difference for secondary outcomes
Dass et al 2008	Rituximab	17	Week 24: 20% reduction in VAS fatigue score	Yes
Meijer et al 2010	Rituximab	30	Weeks 5, 12, 24, and 48: improvement in the stimulated whole saliva flow rate	Yes; significant improvement in weeks 5 and 12
Devauchelle-Pensec et al 2014 TEARS	Rituximab	122	Week 24: 30-mm improvement in two of four VASs	No; but efficacy on secondary end-points
Brown et al 2014 TRACTISS	Rituximab	110	Week 48: 30% improvement in VAS fatigue or oral dryness score	Ongoing

included 17 patients and suggested that, among the various symptoms, fatigue was the most likely to be improved by rituximab, even if the primary end-point was not met [41]. The second study, performed in the Netherlands, included 30 patients (ten placebo, 20 rituximab) and reported that the stimulated salivary flow rate was improved six months after the infusions [42] in the rituximab arm, but not in placebo-treated patients. Two larger trials were then conducted: the multicentre TEARS trial in France [43] and the TRACTISS trial in the UK (which was recently completed but data are not yet available) [44]. The TEARS study included 120 patients with either recent active disease (less than ten years from disease onset and biological markers of B-cell hyperactivity) or systemic involvement. Patients received either two infusions of 1 g of rituximab or a placebo. Its primary end-point (at least 30 mm improvement of at least two among four visual analogic scales (VAS) assessing global activity, dryness, fatigue, and pain) was not met by the study's completion (week 24), but only at the earlier time point (week 6). However, several other secondary outcome measures were improved, notably salivary gland ultrasonographic abnormalities [45], raising the possibility that the pre-defined primary end-point was not able to measure a positive effect of the treatment.

Belimumab

Belimumab is a monoclonal antibody targeting BAFF. It has demonstrated its efficacy in the treatment of systemic lupus erythematosus. The BELISS is an open-labelled trial that

evaluated efficacy of belimumab in 30 patients with pSS with anti-SSA and either current systemic complications or salivary gland enlargement, or early disease (< 5 years), or biomarkers of B-cell activation [46]. The primary end-point, assessed at week 28, was the improvement in two of five items: reduction in ≥ 30% of patients in the dryness VAS score, ≥ 30% in fatigue VAS score, ≥ 30% in VAS pain score, ≥ 30% in systemic activity VAS assessed by the physician, and/or > 25% improvement in any B-cell activation biomarker values. The primary end-point was achieved by 60% of the patients. Improvement of both patient symptoms (measured by ESSPRI) and systemic complications (measured by ESSDAI) was observed. The salivary flow and Schirmer's test did not change. These results were encouraging, but need to be confirmed in an RCT.

Other targeted therapies

The ASAP trial has evaluated the efficacy of abatacept (CTLA4-Ig) in 15 patients with active disease [47]. Patients were treated, in an open-label manner, with eight intravenous abatacept infusions on days 1, 15, and 29 and every four weeks for 24 weeks. A significant improvement in both patient symptoms (measured by ESSPRI) and systemic complications (measured by ESSDAI) was observed. Salivary and lacrimal gland function did not change. After treatment discontinuation, the patient's symptoms and disease activity increased again in the follow-up. An RCT is currently ongoing to confirm these encouraging results.

Hydroxychloroquine

Hydroxychloroquine is a key treatment of systemic lupus erythematous and, based on a similar pathophysiology, is frequently used to treat pSS; however, the evidence supporting its efficacy is inconsistent. In the JOQUER trial, 120 individuals with SS were randomized to receive hydroxychloroquine or placebo for 24 weeks [48]. Following week 24, all participants received hydroxychloroquine between weeks 24 to 48. Response criterion was defined as an improvement of at least 30% of two of the following VAS dryness, fatigue, and pain. There was no significant difference between the two groups at either the 24- or 48-week point. This study demonstrates the limited efficacy of hydroxychloroquine in treating pSS. However, the study end-point includes only three domains, and participants were allowed to continue other medications. Also, patients from this trial were inactive or low active disease, and only a small proportion suffered from inflammatory arthralgia or arthritis, which preclude any conclusion in this specific population where hydroxychloroquine is frequently used. Also, the potential long-term utility of this treatment in SS remains to be assessed.

Ongoing trials and future hopes

We are on the eve of the development of specific therapies for pSS. Several public-funded and industrial RCTs are being launched to test well-known drugs in other indications such as tocilizumab (ETAP study in France) and abatacept (ASAPIII study in the Netherlands), or innovative drugs such as anti-BR3, anti-ICOS-L, anti-CD40 monoclonal antibodies, or lymphotoxin beta inhibition. Table 7.3 summarizes ongoing studies in pSS declared on ClinicalTrials.gov. Therefore, this is an exciting time in the domain of pSS care and research with 10 controlled studies anticipated to be completed in the next 5 years.

Table 7.3 Ongoing studies in pSS						
Study	Drug	Sponsor	Number of subjects	Inclusion criteria	Primary end-point	Estimated completion
NCT01552681	Baminercept, Lymphotoxin-beta Receptor Fusion Protein	National Institute of Allergy and Infectious Diseases	72	Stimulated salivary flow ≥ 0.1mL/min Systemic (inc. fatigue and pain)	Change in stimulated whole salivary flow at W24	May 2015
NCT02291029	CFZ 533, anti-CD40 monoclonal Ab	Novartis	30	ESSDAI ≥ 6	ESSDAI change W12	July 2016
NCT02334306	AMG 557/MEDI587, anti-ICOS-L monoclonal Ab	MedImmune/ Amgen	42	ESSDAI ≥ 6 Anti-SSA/SSB and IgG> 16 g/L or RF +	ESSDAI change D99	November 2016
NCT01782235 ETAP	Tocilizumab Phase 3	Strasbourg University	110	ESSDAI ≥ 5 Anti-SSA/SSB	Improvement ESSDAI ≥3	March 2017
NCT02149420	VAY 736, anti-BAFF-R monoclonal Ab	Novartis	30	ESSDAI ≥ 6 ANA (≥ 1:160) Anti-SSA/SSB Sal. flow> 0	ESSDAI change W12	June 2017
NCT02067910 ASAPIII	Abatacept Phase 3	Gröningen University and BMS	88	ESSDAI ≥ 5 Disease duration ≤ 7 Pathologic parotid biopsy	ESSDAI W24	July 2018
Data from https://clinicaltrials.gov, as of 16 April 2015.						

Trial designs: inclusion and response criteria

Until now, all published RCTs focused on main pSS symptoms (sicca, fatigue, pain), but since the development of the ESSDAI, all new trials focus on systemic involvement. These are very important points to consider: should we target the common symptoms and develop drugs which could virtually improve all pSS patients, or should we focus on systemic involvement which concerns a subpopulation of the patients with the hope of showing more readily an improvement in a short timeframe? Are we willing to prescribe biologics for dryness, fatigue, and diffuse pain, or do we need to keep these drugs for the more severe cases? These considerations involve both inclusion criteria in trials and primary end-points measured.

What is critical is finding out the true prevalence of systemic involvement in pSS. When considering large registry, at a specific time-point approximately 30% of patients present systemic complications; during the disease life-time almost 70% had or will present a clinically significant systemic complication; and almost 90% of patients might present one complication if defined as ESSDAI score ≥ 1 at any time during the disease course [13, 49]. But at a specific time-point, only 15% of the patients in a large multicentre Italian cohort displayed a severe systemic involvement justifying the use of immunosuppressants [50]. Thus, inclusion criteria requiring at least moderate activity (for example, defined as ESSDAI ≥ 5 or 6), biologic activity and recent-onset disease might minimize the ability to recruit patients for clinical trial, as shown recently in the ASSESS cohort [51]. Nevertheless, as discussed earlier, this population is probably the target population of biological therapies.

Also, as mentioned previously, patients with highly active and severe systemic involvement (such as kidney involvement with renal function alteration, neuropathy or myositis with severe motor deficit, inflammatory lung disease with altered pulmonary functional test, etc), in whom the beneficial effect of an active treatment would probably be easier to detect, cannot be included in placebo-controlled trials if there is a risk of organ damage or even a fatal outcome. Only prospective registries could address the issue of efficacy of treatment for these severe patients.

Nevertheless, we must emphasize the trials focusing on the symptoms and those focusing on systemic activity should not be exclusive. In pSS patients, the low quality of life is mostly driven by the patient-reported outcomes such as sicca scores or ESSPRI than by the ESSDAI [52]. Also, post-hoc analyses of the TEARS study and the development of the SSRI suggested that rituximab might be more effective on these symptoms than on the systemic activity when considering patients with low or moderately active patients, i.e. those that can be included in placebo controlled trials. These observations will have to be confirmed in other ongoing trials, and if proven useful, the use of patient-reported outcomes as a primary end-point could be reconsidered.

Finally, once several large trials assessing various drugs in pSS have been completed, it will provide valuable data for the development of more generalized response criteria, similar to the development of the American College of Rheumatology response criteria for rheumatoid arthritis 20 years ago [29,30].

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Chapter 8

Lymphoma: Pathogenesis, prediction, and therapy

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Key points

- The prevalence of non-Hodgkin's lymphoma (NHL) in primary Sjögren's syndrome (pSS) is 3.4% to 7%.
- There is a 20 times increased life-time risk for a pSS patient to develop NHL compared to the general population.
- Risk factors for NHL development include recurrent salivary gland swelling, hypocomplementaemia, leucopenia, cryoglobulinaemia, presence of ectopic germinal centres, and high focus scores on diagnostic minor salivary gland biopsy.
- Identifying the lymphoma type and accurate staging are important for management and prognosis.
- Genetics and chronic antigen-driven immune reactions are important factors in NHL development in SS.
- The optimal treatment for mucosal associated lymphoid tissue (MALT) lymphoma remains under debate.
- Lymphoma account for 20% of SS mortality. Prognosis is better with MALT lymphoma than diffuse large B-cell (DLBC) lymphoma.

Introduction

The development of non-Hodgkin's lymphoma (NHL) is the most severe consequence in primary Sjögren's syndrome (pSS), impacting on disease prognosis, mortality, and morbidity [1]. Characteristically, lymphomas develop within the affected salivary glands, mostly the parotid glands, however, the orbital annexa [2], stomach [3], and lymph nodes can also be affected, with the latter associated with poor prognosis [4].

NHL detection can be incidental, when diagnostic salivary gland biopsy is performed in the major salivary glands [5]. More often, NHL is diagnosed following investigations of patients with clinical suspicion of lymphoma. However, recognizing NHL development in pSS remains a challenge. NHL share clinical features common to pSS extra-glandular manifestations and histologically the disease expand within the dense lymphocytic infiltrate typical of pSS. Nonetheless, rheumatologists should be familiar with the clinical and laboratory signs associated with NHL development, organize the appropriate tests for tumour diagnosis and staging, and provide the patients with general information on prognosis.

Epidemiology

The prevalence of NHL in pSS is 3.4% to 7% [6, 7, 8]. In departments that routinely use parotid gland biopsy for diagnosis of pSS, the prevalence of lymphoma can reach 11% [9]. The life-time risk for a pSS patient to develop NHL is estimated to be 20 times higher than the general population [10]. Previous reports of higher risk (~40 times) were most likely due to selection bias [11]. Nevertheless, the risk of NHL development in pSS patients is higher than in systemic lupus erythematosus and rheumatoid arthritis [10], and correlate with disease duration, with prevalence ranging from 3.4% in the first five years to 9.8% at 15 years [12].

PSS-associated lymphomas are predominantly B-cell malignancies. The mucosal associated lymphoid tissue lymphoma (MALT-L) is the most common type, followed by the diffuse large B-cell lymphoma (DLBC-L) and the nodal marginal zone B-cell lymphoma. The risk of developing MALT-L is higher than the risk of developing DLBC-L (28 versus 11 times) [13]. Indolent types such as the MALT-L may evolve toward the more aggressive histologic types. Often the development of DLBC-L in pSS is the consequence of MALT-L progression [12]. Men are at higher risk than women (odds ratio 2.4, 95% confidence interval (CI): 1.5–3.8 compared to odds ratio 1.3, 95% CI: 0.9–1.9), despite the higher prevalence of pSS among females [14].

Predictive and risk factors

Since the first description of the connection between NHL and pSS, a series of studies using different cohorts have identified several risk factors for NHL development (Box 8.1). Early studies implicated recurrent swollen salivary glands (Figure 8.1), lymphadenopathy, and leg ulcers as risk factors [7]. Later studies have identified additional clinical and laboratory findings that are associated with increased risk of NHL development, among which the presence of palpable purpura and low C4 levels [8, 15, 16]. Neutropenia and cryoglobulinaemia at the time of pSS diagnosis is also associated with an increased risk of lymphoma development [17]. Invariably many of these findings often co-exist such as lymphopenia and parotid gland enlargement [17]. Similarly, anaemia, lymphopenia, thrombocytopenia, hypergammaglobulinaemia, monoclonal components, and cryoglobulinaemia all correlate significantly with the presence of extra-glandular manifestations such as purpura, lymphadenopathy, and splenomegaly.

In a large Spanish cohort of pSS patients the presence of anaemia, leukopenia, lymphopenia, hypergammaglobulinaemia, and low C3 have been identified as predictors of

Box 8.1 Risk factors for NHL development in pSS [8]

- Recurrent salivary gland swelling
- Extra-glandular manifestations*
- Monoclonal gammopathy
- Reduced serum levels of complement C4
- CD4+ lymphocytopenia
- Sharp increase in IgG
- Cryoglobulinaemia
- Low CD4+/CD8+ T cell ratio
- Presence of GC-like structures in salivary gland biopsy

*Purpura, vasculitis, renal involvement, peripheral neuropathy.

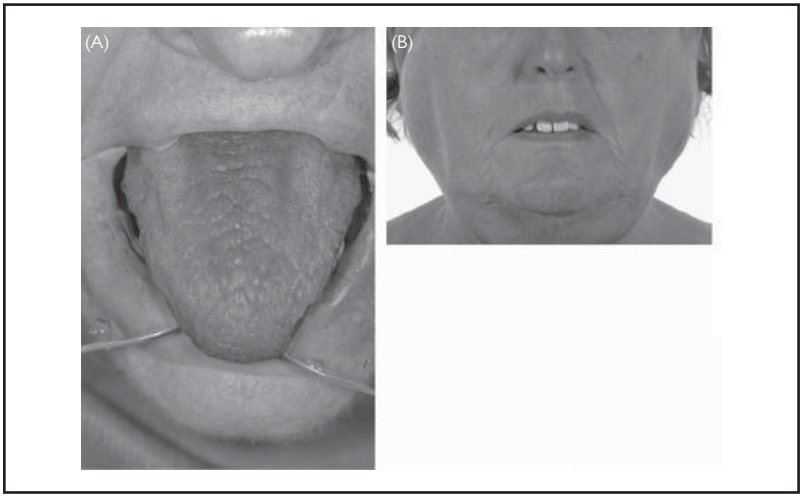

Figure 8.1 Patient with pSS and MALT lymphoma of the salivary gland showing fixed asymmetric swelling of the parotid gland. Original magnification 10 x.

NHL, but only hypo-complementaemia and lymphopenia were independent risk factors for NHL development [12]. Hypo-complementaemia, in particular, is associated with earlier development of NHL and higher mortality [12]. Lymphopenia strongly correlates with the development of DLBC-L [5].

Based on a combination of these risk factors it is possible to stratify pSS patients into two categories: type I pSS patients characterized by hypo-complementaemia, lymphopenia, and cryoglobulinaemias with high risk for lymphoma development and type II pSS patients with an uncomplicated disease course [15].

Another risk factor for lymphoma development is the presence of germinal centre (GC)-like structures in salivary gland biopsies from patients with pSS (Figure 8.2). The potential prognostic value of GC-like structure for NHL development was first suggested in 1999 by Voulgarelis [6], however, epidemiological evidence supporting this association has only been generated recently by an retrospective study conducted by Theander et al [18].

The frequency of GC detection in minor salivary glands biopsies in pSS ranges between 10% and 25%. Patients with GC in the salivary glands are characterized by higher levels of autoantibodies (rheumatoid factor, anti-Ro, and anti-La), a higher degree of B-cells activation (IgG levels), and higher systemic disease activity as measured by the ESSDAI (Box 8.2)) [19, 20].

The relationship between the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) at the time of diagnosis and lymphoma development is still under evaluation. A study of 195 patients analyzed with a median follow-up of 92 months (range 12–256) was unable to establish a correlation between high ESSDAI and lymphoma development. However, the presence of IgM-kappa clonal component, parotid gland enlargement, and low C4 (parameters evaluated in the ESSDAI) were associated with lymphoma development [26]. However, it is extremely difficult to determine whether these clinical manifestations are related to active pSS or consequence of malignant clonal expansion. For example, the elevated serum-free light chains are found in ~30% of NHL. On the other hand, purpura and peripheral neuropathy were recognized

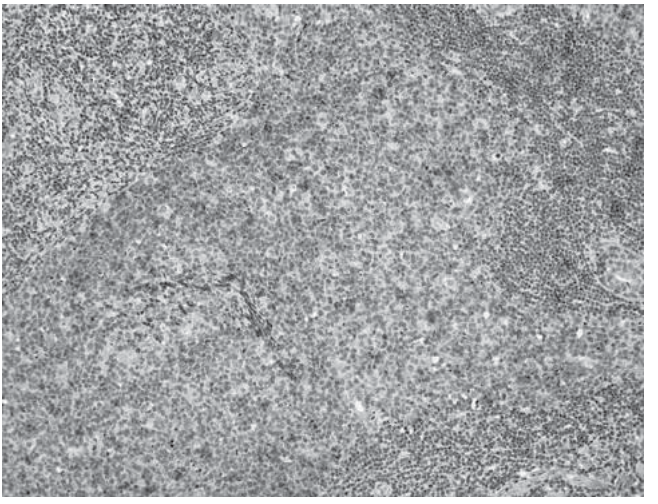

Figure 8.2 Histology of a salivary gland biopsy from a pSS patient showing the presence of a germinal centre (black arrow) within a large inflammatory aggregate.

paraneoplastic manifestations, but were not recognized as independent risk factor for NHL development [26]. Recent studies using multivariate analysis show that high ESSDAI scores correlate with increased beta2-microglobulin, kappa and lambda-free light chain and B-cell activating factor (BAFF) in the serum; parameters known to be increased during NHL development [27]. Interestingly, the ESSDAI score remains higher in patients with lymphoma after treatment compared to pSS patients without NHL.

Diagnosis and staging

Identifying the lymphoma type and accurate staging are important for management and prognosis. Clinical detection of hard, fixed enlargement of the salivary gland, with or without constitutional symptoms (less common in non-aggressive forms) (Box 8.2) should prompt investigations for lymphoma development [28]. The current recommendation for the evaluation of a patient with suspected NHL is to confirm the diagnosis and NHL type using the World Health Organization (WHO) classification followed by staging using both the Ann Arbor staging system (Box 8.3) and the International Prognostic Index (IPI) (Box 8.4) [29].

The WHO classification of lymphoma requires extensive immunophenotyping, often include cytogenetic, fluorescent in situ hybridization (FISH), and studies of the receptor gene rearrangement by polymerase chain reaction (PCR). These investigations require the analysis of excisional biopsy of the affected area by experienced hematopathologists [30]. Large cutting-needle biopsies can be used if the excisional biopsy is deemed difficult or dangerous because of the location or other clinical reasons. Fine-needle biopsies may not provide sufficient information and an open biopsy is often necessary to confirm the diagnosis [31].

Box 8.2 ESSDAI and NHL

The ESSDAI (European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index) represents a useful tool to determine disease activity in patients with pSS and provides a specific and valid measure outcome in clinical trials [21, 22]. Twelve different organ-specific 'domains' contributing to disease activity have been identified and for each domain three or four levels of severity have been recognized. Each domain in the ESSDAI has its own weight and after calculation, a single domain needs to be multiplied for its weight. The final ESSDAI index comes from the addiction of the scores belonging to different domains, with the final calculated score between 0 to 123. A moderately active disease is defined as an ESSDAI ≥ 5. When retesting the patient, the minimal clinically important improvement is expressed as a decrease of at least 3 points. High ESSDAI scores have been associated with malignancy development [23] and, in patients with pSS and established lymphoma with a worst prognosis [24]. The activity items included in ESSDAI are considered if they appeared within the last 12 weeks. For the purpose of this chapter we will discuss the items more likely to change and being affected by the development of NHL. Those include mainly two of the three different categories of the ESSDAI domains: the serological abnormalities and clinical evidence of B-cell activation. Single-organ involvement (kidney, lungs) is rarely subject to change in NHL.

The *constitutional symptom domain* encompasses the presence of fever, mild (37.5°C–38.5°C) or elevated (>38.5°C), involuntary weight loss, and nights sweats. In particular, the onset of severe recurrent fever (at least twice in a week) associated with an important recent weight loss (>10% of body weight) and night sweats is highly suggestive of the presence of lymphoproliferative disease. The *lymphadenopathy domain* is also likely to be affected by NHL development. This domain is scored on the basis of the size of the lymph nodes, which is often difficult to assess clinically. A high score is given to the clinical evidence of current malignant B-cell lymphoma. Current cell malignant disorder should be taken into account except for those in remission for more than six months. Ultrasound assessment is recommended in case of lymphoadenopathy to accurately measure the size and nature of the lymph nodes. It is advisable for clinicians to repeat such diagnostic procedure over the course of patient disease. Salivary gland swelling measured in the *glandular domain* is highly suggestive of B-cell lymphoma. In this section clinicians are called to report on the recent appearance of glandular swelling, including parotids, submandibolar, and lacrimal glands. For lymphadenopathy the grade of severity is scored on the basis of the size of the tissue: 'low' when the diameters of parotid, submandibular, and lacrimal glands are below 3 cm, 2 cm, and 1 cm, respectively, and 'moderate' when they exceed these values. While the role of salivary gland ultrasound is recognized in early pSS diagnosis, it fails to provide a reliable instrument to assess the size of the glands [25]. The laboratory features considered in ESSDAI are divided in two domains: *haematological* and *biological*. In the former, cytopenia is taken into account and, if present, the patient is scored as having 'low', 'moderate', or 'high' activity according to the severity of neutropenia, lymphopenia, anaemia, and thrombocytopenia. Into the biological domain, hypocomplementemia, cryoglobulinemia, and hypergammaglobulinemia are considered and divided into different levels, depending on their entity. Also the recent onset of a sudden hypoglobulinemia (<5g/l), which is a possible sign of alarm for undergoing B-cell malignant proliferation, is considered into the ESSDAI and classified as 'moderate' activity.

Box 8.3 Ann Arbor Staging System

The Ann Arbor Staging System uses Roman numerals to distinguish the stages I–IV (1–4). Lymphomas that affect an organ outside the lymph system (an extranodal organ) have E added to their stage (for example, stage IIE), while those affecting the spleen have an S added.

Stage I
- The lymphoma is in only one lymph node area or lymphoid organ such as the thymus (I).
- The cancer is found only in one area of a single organ outside of the lymph system (IE).

Stage II
- The lymphoma is in two or more groups of lymph nodes on the same side of (above or below) the diaphragm (the thin band of muscle that separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes (II).
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.

Stage III
- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIISE).

Stage IV
- The lymphoma has spread outside the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain, or spinal cord, or the pleura (thin lining of the lungs).

Other modifiers may also be used to describe the lymphoma stage:

Bulky disease

This term is used to describe tumours in the chest that are at least one third as wide as the chest, or tumours in other areas that are at least 10 cm (about 4 inch) across. It is usually designated by adding the letter X to the stage. Bulky disease might need more intensive treatment.

A v B—Each stage may also be assigned an A or B. The letter B is added (for example, stage IIIB) if a person has any of the B symptoms listed below:
- Loss of more than 10% of body weight over the previous six months (without dieting).
- Unexplained fever of at least 38.6°C.
- Drenching night sweats.

These symptoms usually mean the disease is more advanced. If a person has any of these, then more intensive treatment is usually recommended. If no B symptoms are present, the letter A is added to the stage.

Small lymphocytic lymphoma (SLL) /chronic lymphocytic leukemia (CLL)

The Ann Arbor Staging System was originally developed for staging Hodgkin's lymphoma. Therefore, clinicians should be aware of the fact that because of its extra nodal localization, MALT lymphoma will be scored as high grade in this system, despite being generally considered an indolent and benign lymphoma. In 1993 the IPI was developed with the aim to provide a better prognostic tool for NHL.

Box 8.4 International Prognostic Index [29]

Prognostic factors
- Age > 60 years
- Performance status > 2
- Lactate dehydrogenase 1x normal
- Extranodal sites > 2

Stage III or IV

Risk category (factors)
- Low (0 or 1)
- Low intermediate (2)
- High intermediate (3)

Full clinical staging includes clinical history, physical examination, and special investigations. Clinically, examination for the presence of parotid gland swellings, enlarged lymph nodes (> 1.5 cm in maximum diameter is considered enlarged), hepatosplenomegaly, and of the respiratory system should be performed. Blood tests should include full blood count, immunoglobulins and electrophoresis, lactate dehydroxygenase, free light chains, and renal and liver function. Screening for hepatitis B and C and HIV is also advisable.

Imaging of the chest, abdomen, and pelvis, most commonly by computed tomography (CT), should be performed. Magnetic resonance imaging (MRI) studies can be used if CT is contraindicated. Imaging of the salivary glands, neck, and regional lymph nodes with MRI is recommended. Positron emission tomography (PET) can also be used. A study comparing MRI and ultrasound (US) against physical examination and fine-needle aspiration cytology for the preoperative assessment of the location and histology of parotid gland tumours showed that only cytology correctly predicted the benign or malignant nature of the tumour in all cases [30]. Certain MRI or US features (incomplete demarcation from normal parotid gland or diffuse lymphoadenopathy) showed a partial predictive value (0.48 and 0.5, respectively) [32]. Contrast CT may be better for the detection of affected lymph nodes whereas MRI is preferred for local involvement within the mucosal organ [33]. Lumbar puncture, cerebrospinal fluid cytology, and bone marrow aspiration are rarely needed for the staging of salivary gland MALT lymphoma, but might be useful in diffuse disease, in patients at high risk of central nervous system involvement or progression to DLBC-L [30]. PET scan, gallium scan, or bone scan can be requested to complete the staging if imaging obtained with conventional CT or MRI does not provide sufficient information or demonstrate suspicious lesions. However, in pSS MALT lymphoma dissemination is rare and therefore these tests are infrequently requested.

Pathogenesis

Genetic

The typical translocation observed in SG MALT-L is the t(14;18)(q32;q21)/IGH-MALT1. This translocation places the MALT1 gene under the control of the IGH promoter. The same translocation, shared by ~20% of NHL lymphoma is also found in MALT lymphoma arising in the liver, skin, ocular adnexa, and lung; but not in MALT lymphomas

of the stomach, intestine, thyroid, or breast [34], indicating an organ specificity for the development of NHL. The reason for this phenomenon is not clear. More recently, a correlation has been found between certain polymorphisms of TNFAIP3, the gene that encodes the A20 protein, and the risk of developing NHL compared to healthy controls (odds ratio: 3.36 (95% CI 1.34–8.42), and to pSS patients without NHL (odds ratio:3.26, (95% CI: 1.31–8.12); P = 0.011). The A20 protein plays a key role in controlling nuclear factor kappa B (NFκB) activation and the polymorphisms appear to induce functional abnormalities in A20, resulting in hyperactivation of the NFκB pathway, promoting proliferation and cytokine/chemokine production that support the survival B-cell clones in the inflammatory/malignant microenvironment within the salivary glands [35].

Autoimmunity

MALT lymphomas are derived from post-germinal centre marginal zone B cells [28]. The recent identification of germinal centre-like structures as biomarkers for MALT lymphoma development strengthen the pathogentic relationship between local immunological activity, disease persistence, and lymphomagenesis in the affected glands. Salivary gland germinal centres, present in up to 25% of pSS patients, provide the machinery for B-cell proliferation and survival, and are the hub for the development of the malignant clones [36]. There is a large body of evidence supporting a link between antigen-driven polyclonal lymphoid reaction in the pSS salivary glands and the monoclonal proliferation that lead to malignant expansion [37, 38]. The presence of highly mutated sequences in the malignant clones further support the relationship between autoimmune reaction and lymphoma development [13]. However, unlike other memory B-cell lymphomas, the presence of ongoing mutations or intra-clonal variations in their rearranged Ig genes suggest a continuous interdependence of the malignant expansion and the autoimmune process that sustain the GCs [39]. In the major salivary glands (more often characterized by larger and better organized GC) it is possible to identify large areas of lymphoepithelial proliferation, or lymphoepithelial sialoadenitis (LESA), which is considered as a premalignant lesion. These areas of lymphocytic and myoepithelial-cell proliferation may represent an additional hub for malignant clone survival [36].

The presence of local B-cell proliferation, supported by local production of lymphotoxin alpha, B-cell survival factors (e.g. BAFF) (Figure 8.3) and hyperactivation of the NFκB pathway, are insufficient to account for the complex process of lymphomagenesis [28]. For instance, NHL development requires the occurrence of specific mutations within the proliferating B cells and other factors, which are currently not completely understood, to support the expansion of the malignant clones over the large number of polyclonal B cells [37, 38].

Pathology

Histologically, MALT lymphomas compose of a heterogeneous B-cell population that includes marginal zone-like lymphocytes (centrocytes), small lymphocytes, immunoblasts, and centroblasts-like cells. The neoplastic cells are generally small to medium sized with moderately abundant clear or pale eosinophilic cytoplasm. Tumour cells are generally negative for IgD, CD5, and CD10, but express IgM, CD20, and Bcl2. IgA or IgG expression is rare in malignant cells. In some cases, the tumour cells (approximately one third) undergo plasma cell differentiation. Neoplastic clones infiltrate the

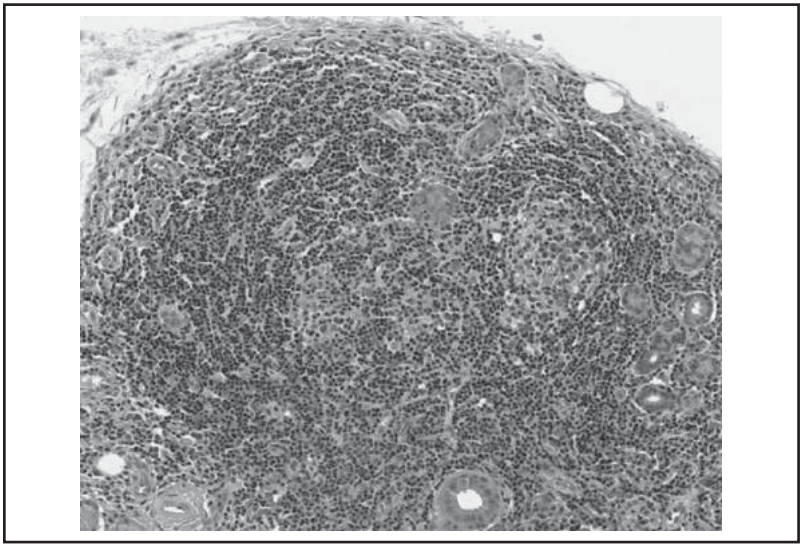

Figure 8.3 Histology of pSS-associated MALT lymphoma showing high level of BAFF expression within a large germinal centre in the reactive area of the lymphoma. Original magnification 10x.

reactive follicles, assuming the characteristic distribution observed in the marginal zone of the spleen and Peyer's Patches. However, the malignant clones can also spread into the interfollicular area [40]. Areas of LESA are often associated with the expansion of the malignant clones [36]. Within the MALT lymphoma it is possible to observe DLBC-L transformation. Clonal transformation suggest a potential pathogenic link between these two lymphoma type, even though different clones identities have been identified in some cases.

Treatment

The therapeutic approach to MALT lymphoma is still debated. While antibiotic therapy is used in helicobacter pylori associated MALT lymphoma of the gut [41], this is not recommended for pSS because a clear association between pathogens and lymphoma development has not been found. There is a general agreement that good control of pSS disease activity with immunosuppressive therapy may prevent NHL development [28]. In cases with no systemic involvement and with lymphoma limited to the salivary gland, watchful waiting is acceptable [5]. Chemotherapy with alkylating agents is recommended for disseminated disease [28]. In established disease radiotherapy is not often recommended as it might exacerbate xerostomia [5, 42]. Rituximab as monotherapy or in combination of conventional chemotherapy has also been used successfully [5,43], often accompanied by improvement in the extra-glandular manifestations of pSS. DLBC-L requires a more aggressive therapeutic approach with CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisolone with rituximab) [44].

Prognosis

In patients with pSS, one fifth of the deaths are attributable to lymphoma [15] and while MALT lymphoma is often considered an indolent and benign malignancy it is still a serious complication and a reason for anxiety for pSS patients. Dissemination to peripheral lymph nodes occurs in one third of the cases, but does not alter the disease outcome [45]. The overall survival rate for patients with MALT-L is estimated between 85% and 95% at five years with progression to more aggressive disease in 10% [46]. Patients with DLBC-L are characterized by shorter survival rates (31 months versus 76 months) [8]. Several factors at diagnosis, including tumour type and stage, can be used to better define prognosis. In a recent retrospective study, high ESSDAI score (>10) was associated with higher risk of mortality (OR 5.241, 95% CI 1.034–26.568), and other adverse outcomes (lymphoma relapse, treatment failure, disease progression, histological transformation) [47]. There is no correlation between the use of immunosuppressive therapy at the onset, type, and prognosis of lymphoma in pSS. Other factors that are associated with increased mortality or adverse events include (i) the lack of improvement in ESSDAI after first line treatment at six months; (ii) a high-intermediate or high IPI score; and (iii) bone marrow involvement, with a high IPI score being the best predictor [47]. Interestingly, the presence of pSS appears not to affect NHL prognosis [48], however, observational studies using larger pSS cohorts treated with novel biological agents may change this perspective.

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Chapter 9

Case studies

Benjamin Fisher

Key points

- Minor salivary gland biopsy has an important role in diagnosis.
- In some cohorts, up to 40% of primary Sjögren syndrome (pSS) cases may be anti-Ro antibody negative.
- The presence of germinal-centre-like structures on minor salivary gland biopsy has been reported to be a risk factor for lymphoma in pSS.
- Arthralgia and rheumatoid factor, sometimes accompanied by low grade synovitis, are common in pSS and may lead to a misdiagnosis of rheumatoid arthritis.
- Fatigue is a common and debilitating symptom in pSS.
- Painful bladder syndrome may be present as part of a chronic pain syndrome that may also encompass features of fibromyalgia and irritable bowel syndrome, or reflect an inflammatory interstitial cystitis.
- Distal renal tubular acidosis occurs in 5% of pSS patients.
- Cough is a common symptom in pSS with multiple causes ranging from bronchial dryness to interstitial lung disease.
- Neuropathy compatible with mononeuritis multiplex or accompanied by cryoglobulinaemia or vasculitis may indicate a greater response to particular immunosuppressive therapies.

Case 1

A 53-year-old woman presented with a six-year history of dry mouth, mild to moderate fatigue, and night sweats. There was no history of rash, arthralgia, or Raynaud's phenomenon. Both unstimulated and stimulated salivary flow rates were 0 ml over five minutes. Despite being little troubled by eye symptoms, she had a Schirmer's test of 5 mm in the right eye and 0 mm in the left eye.

Blood tests:

- Routine chemistry, bicarbonate, and full blood count normal
- IgG 12.4 g/L; protein electrophoresis normal
- ANA 1:1600
- Antibodies to ENA and dsDNA negative

Salivary gland ultrasound showed a diffusely heterogeneous echotexture with numerous hypoechogenic areas and hyperechogenic bands, in both parotid and submandibular

glands (Figure 9.1a). No abnormal lymph nodes were detected. A lip biopsy obtained four minor salivary glands with findings as follows (Figure 9.1b):

- Total glandular surface area 22 mm
- Total number of nodular lymphoid aggregates = 12 (five of which were adjacent to normal appearing acini) of which none have germinal centres
- Moderate patchy atrophy with extensive fat replacement
- Moderate, patchy plasma cell infiltrates
- A few lymphocytes are seen within duct epithelium

Conclusion: These minor salivary glands show significant atrophy and fat replacement. Despite this there are lymphoid aggregates in proximity to normal appearing acini, and this pattern can be regarded, at least focally, as amounting to focal lymphocytic sialadenitis (FLS) as seen in Sjögren's syndrome, with a focus score of 2.2 (including all aggregates).

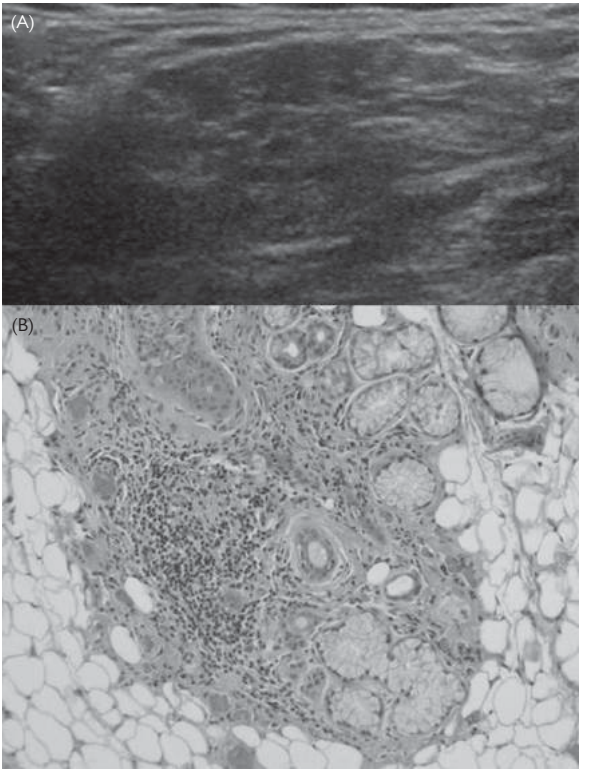

Figure 9.1 (A) Ultrasound of left submandibular gland shows heterogeneous echotexture with multiple hypoechoic areas surrounded by hyperechoic bands. (B) Despite the presence of extensive atrophy and fat replacement, some lymphocytic foci are adjacent to normal appearing acini and ducts. This is important as such atrophic features can be accompanied by lymphocytic infiltration and even foci, in the context of a non-specific chronic sialadenitits.

Despite the absence of anti-Ro and anti-La antibodies, this woman fulfils the 2002 American European Consensus Group (AECG) classification criteria for primary Sjögren's syndrome (pSS) by having a positive minor salivary gland biopsy. This case emphasizes the importance of biopsy for diagnosis, and in some cohorts up to 40% of pSS patients are anti-Ro antibody negative [1]. Although the biopsy shows moderate atrophy and extensive fat replacement, the presence of lymphocytic foci adjacent to normal acini is consistent with the characteristic feature of pSS histology: FLS. The atrophic features may simply represent co-existent, non-specific chronic sialadenitits, which is common in the population [2], although in this case it may reflect an end-stage of longstanding primary Sjögren syndrome (pSS). Certainly, in common with many newly diagnosed patients, there is a long history of symptoms preceding diagnosis, with the delay arising through lack of familiarity of pSS or attribution of symptoms to another disorder or age-related phenomenon.

The diagnosis of pSS is supported by characteristic ultrasound findings, although are not part of any classification criteria as of yet. The case for including ultrasound in such criteria is hampered by lack of standardization, a probable lower diagnostic sensitivity than biopsy, and unclear sensitivity in early disease. Recent evidence also suggests that some biopsy features may have prognostic value in relation to lymphoma risk, in particular the presence of germinal centres and higher focus scores [3, 4].

Symptomatic treatment for the dry mouth consisted of oral lubricating gel with a number of alternative preparations suggested. Meticulous oral hygiene was encouraged with high fluoride toothpaste (5000ppm) and alcohol-free mouthwash. Beyond this, a trial of pilocarpine could be considered, started at 2.5 mg bd, and increasing on a monthly basis to 5 mg tds or even qds. However the atrophic findings on the minor salivary gland biopsy, the advanced change on ultrasound, and the absence of saliva on testing, suggest that this would be unlikely to be successful. European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score [5] was 0, indicative of no obvious systemic disease involvement.

Case 2

A 57-year-old woman was referred by her dentist with recurrent dental caries, resulting in the loss of five teeth. She described a 20-year history of dry mouth symptoms and mildly gritty eyes. She was intolerant of curries and strong alcoholic beverages due to a burning sensation in her mouth. She also described fatigue and arthralgia, particularly affecting her hands and feet. There was no history of rash. She was negative for anti-nuclear antibody (ANA) and anti-Ro and anti-La antibodies, and other blood tests, including immunoglobulins and complement levels, were also within normal limits. Minor salivary gland biopsy revealed a prominent focal lymphocytic sialadenitis and germinal centre formation, and she was diagnosed with pSS. She was managed with oral lubricating gel and pilocarpine 5 mg bd, and used carmellose eye drops occasionally. Hydroxychloroquine 200 mg od was added for arthralgia and the patient reported this to be of benefit. She also took thyroxine for autoimmune hypothyroidism, and smoked six cigarettes a day.

Seven years later she developed a small rubbery lump on the surface of her palate which ulcerated. She was not otherwise symptomatic and did not seek medical attention until she developed multiple tender and enlarged lymph nodes in her neck. She had no 'B symptoms'.

Imaging revealed a large right palatal soft tissue mass with bilateral cervical, supraclavicular, right costophrenic, right hilar, and subcarinal lymphadenopathy. Biopsy confirmed a diffuse large B-cell lymphoma with staging IIA. She was treated with six cycles of R-CHOP and additional intrathecal methotrexate. She had a rapid response and a PET-CT scan two months after completion of therapy showed her to be in remission, which is ongoing. For two years post treatment she noticed considerable improvement in her fatigue and sicca symptoms, although these subsequently returned.

This case raises a number of interesting issues. Various clinical findings have been associated with higher lymphoma risk, and these include salivary glands enlargement, lymphadenopathy, palpable purpura, cutaneous vasculitis, peripheral neuropathy, low complement levels, and cryoglobulinaemia. The combination of palpable purpura and low C4 is said to be associated with particularly high risk. None of these factors were present in this case, but germinal centre-like structures were noted on salivary gland biopsy, which, as stated in Case 1, appear to be a risk factor for lymphomagenesis.

The patient was aware of lymphoma being associated with pSS, but did not consider this until she later developed cervical lymphadenopathy, which is informative for patient education. Considerable improvement in pSS symptoms occurred following chemotherapy, which is often reported anecdotally. This may reflect use of rituximab, although current evidence for efficacy is mixed. However, older, small case series also suggested symptomatic and histological improvement with cyclophosphamide, although this could not be recommended for the management of sicca. Whilst the patient was clear that hydroxychloroquine was beneficial for her arthralgia, the evidence supporting its use in this setting remains anecdotal with support from case series. A small, double-blind cross-over trial and a larger more recent randomized controlled trial have failed to provide support [6].

Case 3

A 42-year-old woman was referred for a second opinion. She first presented at the age of 17 with joint pain and swelling and was diagnosed as having rheumatoid arthritis. She was initially managed with penicillamine but developed pancytopenia. She was subsequently treated with methotrexate, hydroxychloroquine, sulfasalazine, and gold, all discontinued due to lack of efficacy, side effects, or low neutrophil count. Following haematological investigations she was diagnosed with autoimmune neutropenia. Non-steroidal anti-inflammatory drugs were associated with gastric intolerance. Oral prednisolone was symptomatically helpful, and was taken for a total of eight years before being discontinued when she was diagnosed with osteoporosis. Since the onset of her joint pains she has also had Raynaud's and dry eyes and mouth, leading to the repeated insertion of tear duct plugs followed by cauterization. She developed pelvic pain relieved by bladder emptying, urinary urgency, and nocturia, with repeatedly negative urine cultures. Symptoms became worse after discontinuation of prednisolone. Cystoscopy showed inflammatory features (Hunner's lesions) and biopsy revealed mucosal oedema and congestion with increased mononuclear cells and prominent mast cells, consistent with interstitial cystitis. Intravesicular botulinum toxin, hyoscine butylbromide, and amitriptyline were ineffective, and cystectomy was considered. At that point she was referred for a second opinion.

Key features remained dry eyes and mouth, fatigue, and widespread joint pain, particularly affecting the hands and feet and morning stiffness lasting one and a half hours. She had had daily night sweats over the previous two years, with weight gain and no fever.

Additional diagnoses included fibromyalgia, irritable bowel syndrome, and depression. Medications included hyaluronate eye drops used hourly, duloxetine for depression, and strong opioids and paracetamol for pain.

On examination, she had tenderness on her wrists and metacarpophalangeal joints bilaterally. Mild swelling was noted on four joints on a 28-joint count. She had mild parotid swelling and small palpable lymph nodes in the left anterior triangle, < 1 cm. Immunology revealed modestly raised IgG at 17g/L and positive anti-Ro and anti-La antibodies. She was negative for rheumatoid factor, anti-CCP, and dsDNA antibodies. X-rays of the hands revealed no erosions and ultrasound showed mild synovial hypertrophy on the wrists with no increased vascularity on power Doppler. Schirmer's test was 4 mm in the right eye and 0 mm in the left and unstimulated salivary flow of 0.4 ml over five mins. ESSDAI score was 10 (constitutional low, glandular low, articular moderate, biological low). She described painful swelling of her parotid gland after eating and a sialogram was organized. This showed no obstruction but did show features of Sjögren's syndrome (Figure 9.2).

Arthralgia with morning stiffness is common in pSS, and in a smaller number of cases may be accompanied by synovitis. This may be misdiagnosed as rheumatoid arthritis, and the presence of sicca symptoms should prompt consideration of pSS. Rheumatoid factor is common in both disorders, but the absence of anti-CCP antibodies and a mild non-erosive synovitis points to a diagnosis of pSS in this case. The absence of a power Doppler signal on synovial ultrasound makes future erosive change unlikely. Typical management would be hydroxychloroquine or non-steroidal anti-inflammatory drugs, although methotrexate or azathioprine could be considered if warranted, and episodic flares could be managed with short courses of prednisolone.

Painful bladder syndrome/interstitial cystitis is characterized by bladder pain relieved by voiding, often associated with other symptoms including urinary frequency, urgency, and nocturia. Symptoms suggestive of this have been reported in 5% of patients with pSS [7]. Numerous treatments have been proposed, in addition to patient education, and these include amitriptyline, cimetidine, bladder hydrodistension, and even ciclosporin [8]. The pathogenesis remains ill-defined, and may be varied, with many cases seemingly part of a symptom complex with fibromyalgia and irritable bowel syndrome.

Figure 9.2 Left parotid sialogram shows a normal calibre parotid duct, but the intraglandular ducts are beaded with multiple small collections of contrast, a characteristic finding in pSS.

However, there are a small number of case reports on pSS where bladder histology reveals lymphocyte infiltration, sometimes responding to prednisolone [9]. A cautious trial of ciclosporin could be considered in this patient, with a view to decreasing opioid requirements and improving quality of life.

Fatigue is a very common symptom in pSS and is associated with psychosocial variables such as pain, depression, and helplessness [10]. Indeed, up to 20% of patients with pSS may also fulfil classification criteria for fibromyalgia. This association remains poorly understood, and whilst it may have been triggered by a primary immunological insult, the widespread pain and polysymptomatology of fibromyalgia should be carefully distinguished from the assessment of inflammatory arthritis, or indeed painful bladder syndrome/interstitial cystitis, to prevent unnecessary escalation of treatment with immunomodulatory or immunosuppressive medications.

Case 4

A 47-year-old woman first presented to a physician seven years previously with dry eyes and mouth, fatigue, and blepharitis. She was noted to be anti-Ro antibody positive and was diagnosed with pSS. Three years later she presented with renal stones and nephrocalcinosis (Figure 9.3), with localized dilatation of her left collecting system on ultrasound. A history of recurrent urinary tract infections followed, together with renal angle pain. These symptoms settled following the removal of two stones through left-sided ureto-renoscopy.

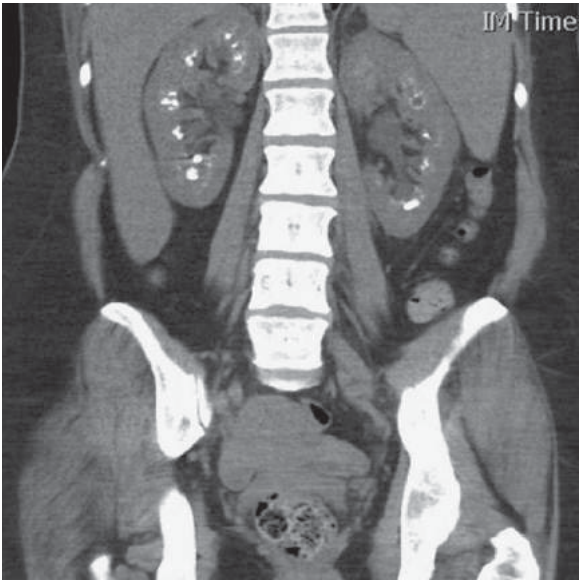

Figure 9.3 CT shows bilateral renal parenchymal calcific foci confined to the medullary areas.

On examination she had an unstimulated salivary flow of 0.24 ml over five mins, Schirmer's test 0 mm in each eye, and mild parotid enlargement. Recent investigations revealed the following:

- Venous pH 7.29
- Creatinine 112 μmol/L (44–80);
- eGFR 45ml/min
- Sodium 135 mmol/L
- Potassium 3.3 mmol/L (3.5–5.3)
- Calcium 2.13 mmol/L (2.14–2.62)
- Chloride 108 (98–110)
- Bicarbonate 13 mmol/L (22–32)
- Urine pH 7.0
- ANA 1:1600
- Anti-Ro and anti-La antibody positive
- Serum IgG 28 g/L, polyclonal
- Minor salivary gland biopsy: focus score = 3.3 with germinal centre-like structures

The presence of renal stones, nephrocalcinosis, low bicarbonate or potassium, high chloride, or persistently elevated urine pH, in a patient with pSS should prompt consideration of distal renal tubular acidosis (dRTA). This has been reported in 5% of patients with pSS, although up to 25% may have incomplete dRTA, characterized by an inability to acidify urine following an acid load, but with normal serum bicarbonate. DRTA is characterized by a normal anion gap (hyperchloraemic) metabolic acidosis. A principal defect is the failure of the distal intercalating cell H^+-ATPase proton pump to secrete hydrogen ions into the lumen, resulting in failure of bicarbonate absorption [11]. Consequently, the urine pH is persistently above 5.3, and often > 6.5, despite the metabolic acidosis. Urine pH measurement should be accompanied by urinanlaysis, and culture if indicated, as urea-splitting organisms such as proteus may also elevate pH.

In pSS, dRTA may be a manifestation of tubulointerstitial nephritis, but has also been associated with antibodies to carbonic anhydrase II [12], which if functional, could prevent the distal intracellular generation of bicarbonate that is normally returned to the blood.

Marked failure of hydrogen ion secretion leads to the secretion of potassium to maintain electroneutrality, and thus hypokalaemia. The metabolic acidosis also leads to buffering by bone through the release of calcium phosphate, leading to hypercalciuria. High urine pH increases calcium precipitation and the formation of calcium phosphate stones. The acidosis also increases proximal tubular reabsorption of citrate, which normally inhibits calcium-stone formation. Nephrocalcinosis occurs through the formation of calcium phosphate deposits in ducts, and may be accompanied by generalized interstitial fibrosis [13].

In this case, the patient had an anion gap of 14 mmol/L (normal 6–16 mmol/L). The presence of nephrocalcinosis and high urine pH despite a marked acidosis makes a diagnosis of dRTA likely, in the context of active pSS. A test of urine acidification was therefore not undertaken. If required, the concomitant administration of furosemide 40 mg and fludrocortisone 1 mg is better tolerated than oral ammonium chloride administration, but may have lower diagnostic efficiency [14].

Although surgically removable stones may comprise a proportion of the nephrocalcinosis in dRTA, as in this case, the focus has to be on correction of the acidaemia to prevent chronic renal damage. Correction of the low bicarbonate with oral sodium bicarbonate, sodium citrate, or potassium citrate, will result in stabilization or even partial reversal of nephrocalcinosis, and a reduction in renal stones, osteoporosis risk, potassium loss, and urinary tract infections. Some authors now consider potassium citrate to be the treatment of choice [15].

The patient had an ESSDAI score of 14 (renal, glandular, and biological domains) suggesting 'high' systemic disease activity, but current practice would manage the dRTA as outlined earlier without initiating immunosuppressive therapy. Nevertheless, the focus score > 3 and with germinal centre-like structures puts her in a higher risk group for lymphoma [3, 4].

Case 5

A 51-year-old woman presented with an 18-month history of dry eyes, a mildly dry mouth, and a dry cough. On direct questioning, she had shortness of breath climbing stairs and walking 200 metres. She also described recent weight loss and arthralgia affecting the small joints of the hands, with morning stiffness lasting two to three hours. There was a past history of hypothyroidism. There was no history of TB.

On examination she had mild parotid enlargement but no lymphadenopathy. Her heart sounds were normal with a rate of 90 beats/minute. She had mild fine inspiratory crackles at her lung bases with no dullness to percussion. Abdominal examination was unremarkable. No synovitis was present on joint examination. Schirmer's test was 1 mm in each eye, but unstimulated salivary flow was 3.3 ml in five minutes.

Investigations revealed the following:

- Urea and electrolytes (U&E), liver function tests (LFTS), full blood count (FBC), and bicarbonate normal
- ESR 44
- CRP 4 mg/L (normal < 10)
- IgG 56 g/L (normal < 16 g/L); polyclonal
- Rheumatoid factor 93 iu/L (normal < 14)
- ANA 1:1600
- Anti-Ro and anti-La antibody positive
- Anti-tTG antibody positive

An ultrasound scan revealed large hypoechogenic areas with hyperechogenic bands in the parotid and submandibular glands, consistent with SS.

The initial presentation is of pSS but raises a number of issues, the most pressing of which is her respiratory system. Cough is a common symptom in pSS and can arise for a number of reasons. Most commonly this is due to tracheal dryness, but other causes include laryngotracheal reflux, airway disease, follicular bronchiolitis, and interstitial lung disease. Cough due to tracheal dryness is associated with impaired mucociliary clearance and can be a difficult symptom to treat; approaches include room humidification, saline nebulisers, bromhexine, or guaifenesin containing preparations, and pilocarpine. Laryngotracheal reflux is important to consider as this may be amenable to intervention [16]. However the presence of shortness of breath on exertion and fine inspiratory crackles suggests the presence of interstitial lung disease.

Pulmonary function tests:

- DLCO 60% predicted
- VA 72% predicted
- DLCO/VA 72% predicted
- TLC 74% predicted

High resolution CT scan of the chest revealed widespread ground glass opacification seen within the mid and lower zones with some traction bronchiectasis and areas of adjacent air trapping. The radiological diagnosis was non-specific interstitial pneumonia (NSIP). Lymphocytic interstitial pneumonia (LIP) was a differential, although the findings were less typical as no cysts or centrilobular nodules were observed.

NSIP is the most common subtype of interstitial lung disease in pSS, followed by LIP, usually interstitial pneumonitis and organizing pneumonia in decreasing order of frequency. NSIP is frequently responsive to steroids, and she responded well to prednisolone at a starting dose of 40 mg daily. Azathioprine was added as a first-line steroid-sparing agent. Mycophenolate, ciclosporin, and rituximab have also been used [17].

Studies have varied in the frequency with which coeliac disease is identified in cohorts of pSS patients, varying from background prevalence to ten-fold increased risk. We screen all newly presenting pSS patients for IgA anti-tTG antibodies, and would pursue duodenal biopsies in this patient once her respiratory disease was stabilized.

She had an ESSDAI score at presentation of 17 (constitutional low, articular low, pulmonary moderate, and biological moderate).

Case 6

A 64–year-old woman had presented 11 years previously with sicca symptoms and peripheral neuropathy. She was anti-Ro and anti-La antibody positive and was diagnosed with pSS. She had had a persistent dry cough with a normal high resolution computed tomography (HRCT) chest, thought to be due to bronchial dryness. There was no history of rash, arthralgia, salivary gland enlargement, or lymphadenopathy, and no other past medical history or medications. Her other blood tests were unremarkable with normal full blood count, bicarbonate, IgG, and complement levels and negative cryoglobulins, ANCA, anti-cardiolipin and neuronal antibodies and hepatitis C serology. A sural nerve biopsy confirmed a predominantly demyelinating neuropathy but showed no evidence of vasculitis. Neuropathy symptoms were considered stable, and she was not started on any immunosuppressive treatment.

On routine follow-up she reported that paresthesias affecting the hands and feet had slowly progressed over a number of years. Medication consisted of twice daily hypromellose 0.3% eye drops and gabapentin 300 mg bd for neuropathic symptoms. Examination revealed decreased sensation below the knees, with reflexes difficult to elicit. Power appeared 4/5 distally in the legs and left hand. Pseudoathetosis was not elicited. Repeat nerve conduction studies revealed absent sensory responses in the limbs consistent with a severe sensory axonal neuropathy. Motor conduction studies and electromyography (EMG) were normal.

A spectrum of peripheral nerve abnormalities occur in pSS (Box 9.1). Axonal sensory polyneuropathy is usually subacute or chronic on onset, and if symptoms are relatively stable, or only slowly progressive, is usually treated symptomatically, with agents such as gabapentin, pregabalin, or duloxetine. A slow titration to therapeutic dose is recommended in pSS to avoid exacerbating fatigue, and this may necessitate three-to-four-month trials of respective agents [18]. Although tricyclic antidepressants (TCAs)

Box 9.1 Peripheral neuropathies associated with pSS

- Ganglionopathies/sensory neuronopathies
- Axonal sensory or sensorimotor polyneuropathy
- Small fibre neuropathy
- Autonomic neuropathy
- Mononeuritis multiplex
- Cranial neuropathies

are best avoided in pSS due to their anti-cholinergic side effects, if needed, these occur less frequently with secondary amine TCAs such as nortriptyline.

If the presentation is acute or asymmetrical then the important differential would be mononeurtitis multiplex, as the vasculitic process responsible may respond well to immunosuppressive therapies [18]. In the absence of these factors, response to immunosuppressive agents is often disappointing. Similarly, in patients with cryoglobulinaemia or vasculitis, rituximab may also be a therapeutic option, but appears to be less effective in neuropathy without these factors [19]. A retrospective study has suggested that IV immunoglobulin may be helpful in pSS-related sensory neuropathy [20], although more data is required, particularly given the expense of this treatment.

The involvement of large fibres, as indicated by reduction in proprioception and also the loss of reflexes, distinguishes this case clinically from a small fibre neuropathy, which may occur in 5% to 10% of pSS patients [18], and which is again treated symptomatically. A differential would be a sensory ganglionopathy. This is often accompanied by pseudoathetosis or sensory ataxia, due to profound loss of proprioception, although this may also occasionally occur in a sensory neuropathy. The distribution of symptoms in a ganglionopathy may also be patchier. The development of apparent weakness in this case is likely due to progressive dysthesia leading to restriction of effort.

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Appendix 1

ESSDAI

Box A1.1 Constitutional domain	
Please take care not to rate constitutional symptoms not related to the disease (e.g. fever of infectious origin, voluntary weight loss)	
No activity	Absence of the following symptoms
Low activity	Mild or intermittent fever (37.5°–38.5°C)/night sweats Involuntary weight loss of 5% to 10% of body weight
Moderate activity	Severe fever (> 38.5°C)/night sweats Involuntary weight loss of > 10% of body weight

Box A1.2 Lymphadenopathy domain	
No activity	Absence of the following features
Low activity	Lymphadenopathy ≥ 1cm in any nodal region or ≥ 2cm in inguinal region
Moderate activity	Lymphadenopathy ≥ 2cm in any nodal region or ≥ 3cm in inguinal region, or Splenomegaly (clinically palpable or assessed by imaging)
High activity	Current malignant B-cell proliferative disorder

Box A1.3 Glandular domain	
Please take care not to rate glandular swellings not related to the disease (e.g. a stone or infection)	
No activity	Absence of glandular swelling
Low activity	Small glandular swelling with: • enlarged parotid (≤ 3cm), • or limited submandibular or lachrymal swelling
Moderate activity	Major glandular swelling with: • enlarged parotid (> 3cm) • or important submandibular or lachrymal swelling

Box A1.4 Articular domain	
Please take care not to rate articular involvement not related to the disease (e.g. osteoarthritis)	
No activity	Absence of currently active articular involvement
Low activity	Arthralgias in hands, wrists, ankles, and feet accompanied by morning stiffness (> 30 min)
Moderate activity	1 to 5 synovitis among a 28 count
High activity	≥ 6 synovitis among a 28 count

Box A1.5 Cutaneous domain	
Please take care not to rate 'no activity' for stable, long-lasting features that are related to damage rather than disease activity, or cutaneous involvement not related to the disease	
No activity	Absence of currently active cutaneous involvement
Low activity	Erythema multiforme
Moderate activity	• Limited cutaneous vasculitis, including urticarial vasculitis, or • Purpura limited to feet and ankle, or • Subacute cutaneous lupus
High activity	• Diffuse cutaneous vasculitis, including urticarial vasculitis, or • Diffuse purpura, or • Ulcers related to vasculitis

Box A1.6 Respiratory domain	
Please take care not to rate 'no activity' for stable, long-lasting features that are related to damage rather than disease activity, or respiratory involvement (e.g. tobacco) not related to the disease	
No activity	Absence of currently active pulmonary involvement
Low activity	• Persistent cough or bronchial involvement with no radiographic abnormalities on X-ray, or • Radiological or HRCT evidence of interstitial lung disease with: • No breathlessness and normal lung function test
Moderate activity	Moderately active pulmonary involvement, such as interstitial lung disease proven by HRCT with: • Shortness of breath on exercise (NHYA II), or • Abnormal lung function tests restricted to: • 70% > DLCO ≥ 40% and/or 80% > FVC ≥ 60%
High activity	Highly active pulmonary involvement, such as interstitial lung disease proven by HRCT with: • Shortness of breath at rest (NHYA III, IV), or • With abnormal lung function tests: DLCO < 40% and/or FVC < 60%

Box A1.7 Peripheral nervous system domain	
Please take care not to rate 'no activity' for stable, long-lasting features that are related to damage rather than activity, or PNS involvement not related to the disease	
No activity	Absence of currently active PNS involvement
Low activity	Evidence of active peripheral nervous system involvement, such as: • Pure sensory axonal polyneuropathy proven by NCTs • Trigeminal (V) neuralgia
Moderate activity	Evidence of moderately active peripheral nervous system involvement, such as: • Axonal sensory-motor neuropathy proven by NCTs with no motor deficit • Pure sensory neuropathy with presence of cryoglobulinemic vasculitis • Ganglionopathy with symptoms restricted to mild/moderate ataxia • Inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (no motor deficit or mild ataxia) • Cranial nerve involvement of peripheral origin (except trigeminal (V) nerve)
High activity	Evidence of highly active peripheral nervous system involvement, such as: • Axonal sensory-motor neuropathy proven by NCTs with motor deficit ≤ 3/5 • Peripheral nerve involvement proved to be due to vasculitis (mononeuritis multiplex, etc) • Severe ataxia due to ganglionopathy • Inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤ 3/5 or severe ataxia

Box A1.8 Muscular domain	
Please take care not to rate muscular involvement not related to the disease (e.g. weakness due to corticosteroids)	
No activity	Absence of currently active muscular involvement
Low activity	Active myositis proven by abnormal EMG or biopsy with: • No weakness and creatine kinase (N < CK ≤ 2N)
Moderate activity	Moderately active myositis proven by abnormal EMG or biopsy with: • Weakness (maximal deficit of 4/5), or • Elevated creatine kinase (2N < CK ≤ 4N)
High activity	Highly active myositis proven by abnormal EMG or biopsy with: • Weakness (deficit ≤ 3/5), or • Elevated creatine kinase (>4N)

Box A1.9 Central nervous system domain

Please take care not to rate 'no activity' for stable, long-lasting features that are related to damage rather than disease activity, or CNS involvement not related to the disease

No activity	Absence of currently active CNS involvement
Moderate activity	Moderately active CNS features, such as: • Cranial nerve involvement of central origin • Optic neuritisMultiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
High activity	Highly active CNS features, such as: • Cerebral vasculitis with cerebrovascular accident or transient ischemic attack • Seizures • Transverse myelitis • Lymphocytic meningitis • Multiple sclerosis-like syndrome with motor deficit

Box A1.10 Haematological domain

For anaemia neutropenia and thrombopenia, only auto-immune cytopenia must be considered. Please take care not to rate 'no activity' for stable, long-lasting features ofcytopenia not related to the disease (e.g. vitamin or iron deficiency, drug-induced cytopenia, as for example lymphocytopenia associated with cyclophosphamide)

No activity	Absence of auto-immune cytopenia
Low activity	Cytopenia of auto-immune origin with: • Neutropenia (1000 < neutrophils < 1500/mm^3), or • Anaemia (10 < Hb < 12g/dl), or • Thrombocytopenia (100,000 < Plt < 150,000 mm^3), or • Lymphopenia (500 < lymphocytes < 1000/mm^3)
Moderate activity	Cytopenia of auto-immune origin with: • Neutropenia (500 ≤ neutrophils ≤ 1000/mm^3), or • Anaemia (8 ≤ Hb ≤ 10g/dl), or • Thrombocytopenia (50,000 ≤ Plt ≤ 100,000/mm^3), or • Lymphopenia (≤500/mm^3)
High activity	Cytopenia of auto-immune origin with: Neutropenia (neutrophils < 500/mm^3) • or anemia (Hb < 8 g/dl) • or thrombocytopenia (Plt < 50.000/mm^3),

Biological domain	
No activity	Absence of any of the following biological feature
Low activity	• Clonal component, or • Hypocomplementemia (low C4 or C3 or CH50), or • Hypergammaglobulinemia or IgG level between 16 and 20g/L
Moderate activity	• Presence of cryoglobulinemia, or • Hypergammaglobulinemia or high IgG level > 20g/L, or • Recent onset hypogammaglobulinemia or recent decrease of IgG level (<5g/L)

Box A1.11 Renal domain	
Please take care not to rate 'no activity' for stable, long-lasting features that are related to damage rather than disease activity, and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first	
No activity	Absence of currently active renal involvement: • Proteinuria < 0.5 g/d, no hematuria, no leucocyturia, no acidosis • Stable, long-lasting stable proteinuria due to damage

Low activity	Evidence of specific active renal involvement, limited to:
	• Tubular acidosis without renal failure (GFR^4 ≥ 60 ml/min)
	• Glomerular involvement
	  • with proteinuria (between 0.5 and 1 g/d)
	  • without hematuria or renal failure (GFR^4 ≥ 60 ml/min)

Moderate activity	Moderately active renal involvement, such as:
	• Tubular acidosis with renal failure (GFR^4 < 60 ml/min)
	• Glomerular involvement
	  • with proteinuria between 1 and 1.5g/d
	  • without hematuria or renal failure (GFR^4 ≥ 60 ml/min), or
	• Histological evidence of
	  • Extra-membranous glomerulonephritis
	  • Important interstitial lymphoid infiltrate

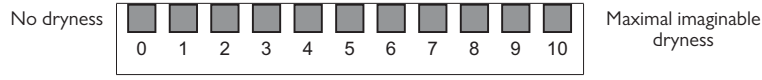
High activity	Highly active renal involvement, such as:
	• Glomerular involvement
	  • With proteinuria > 1.5 g/d, or
	  • Hematuria, or
	  • Renal failure (GFR^4 < 60 ml/min), or
	• Histological evidence of
	  • Proliferative glomerulonephritis
	  • Cryoglobulinemia related renal involvement

Scoring: Each domain is given a score of 0 (no activity), 1 (low activity), 2 (moderate activity), or 3 (high activity). Each domain score is given a weighting according to its relative contribution to the overall disease activity. The total score is the sum of the weighted domain scores.	

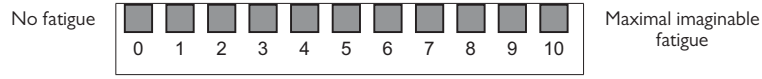
Appendix 2

ESSPRI

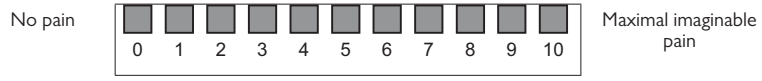
(1) How severe has your **dryness** been during the last two weeks?



(2) How severe has your **fatigue** been during the last two weeks?



(3) How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last two weeks?

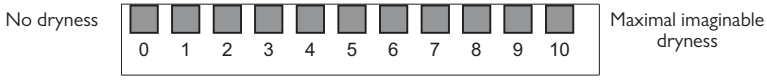


Scoring: Average score for (1), (2), and (3):

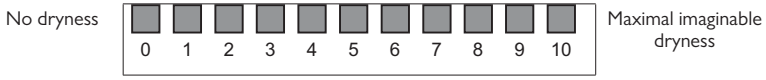
Appendix 3

EULAR sicca score

(1) How severe has your **ocular** (eye) **dryness** been during the last two weeks?



(2) How severe has your **oral** (mouth) **dryness** been during the last two weeks?



Scoring: [(1) score + (2 x (2) score)]/3

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Note to index: *b* following the page number denotes a box, *f* a figure, and *t* a table

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